ROUTES TO SIMPLE 3-SUBSTITUTED OXETANES

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by

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SEAN P.W. CAROLAN

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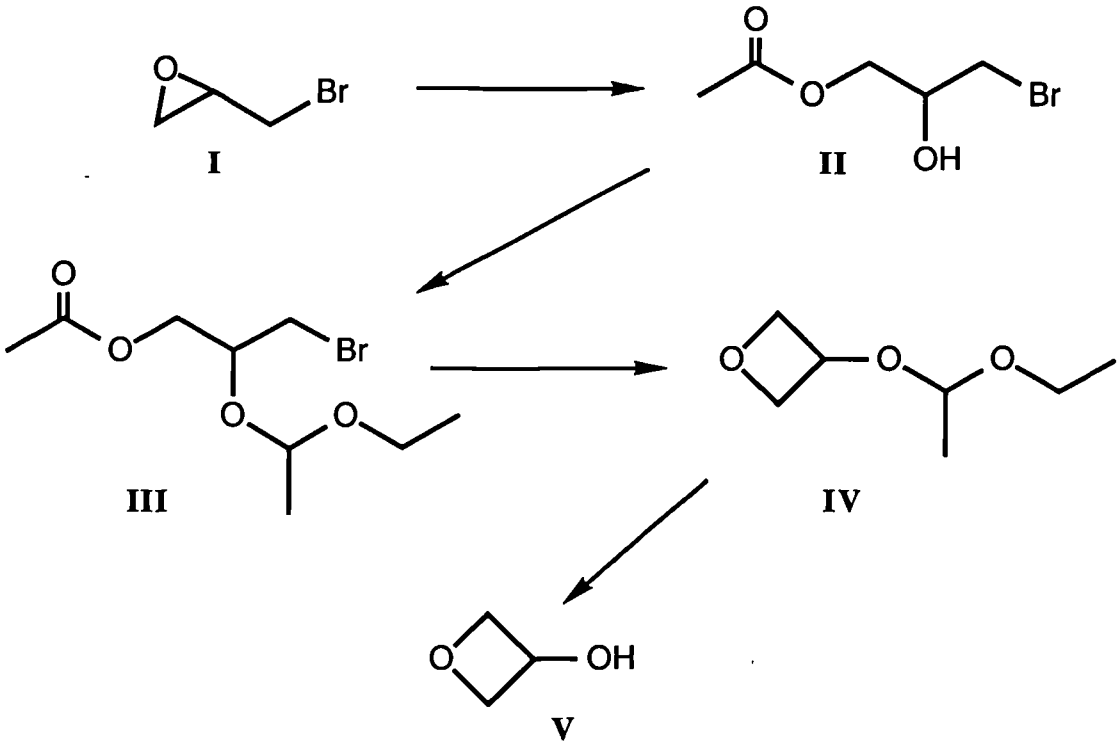
SUMMARY

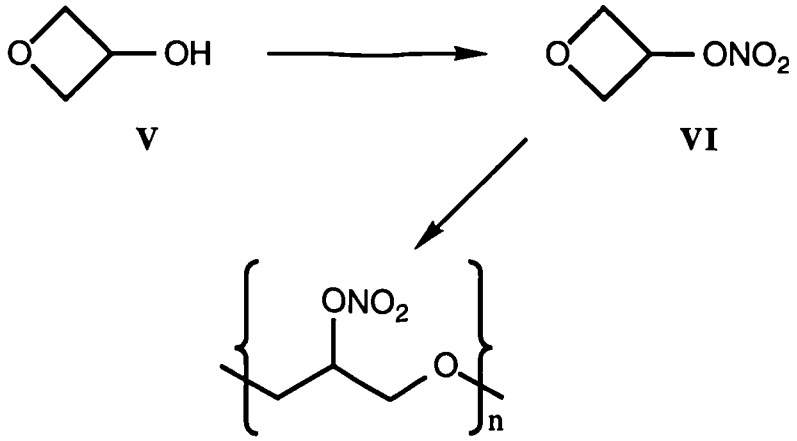
SUMMARY

This thesis describes syntheses and attempted syntheses of certain 3-substituted oxetanes. Simple oxetanes bearing reactive substituents in the 3-position are required since the polymerisation of these compounds is anticipated to lead to polymers of potential use as energetic binders in rocket propellant systems. Oxetanes of particular interest are 3-hydroxyoxetane, 3,3-bis(hydroxymethyl)oxetane, and 3-(hydroxymethyl)oxetane.

3-Hydroxyoxetane was prepared in three steps from epibromohydrin (**I**). Firstly, Lewis acid-catalysed ring opening of the epoxide in the presence of acetic acid gave the bromohydrin **II**. This was heated with ethyl vinyl ether and *p*-toluenesulphonic acid, and cyclisation of the resulting ether **III** with strong base afforded the oxetane **IV**. Deprotection gave 3-hydroxyoxetane (**V**).

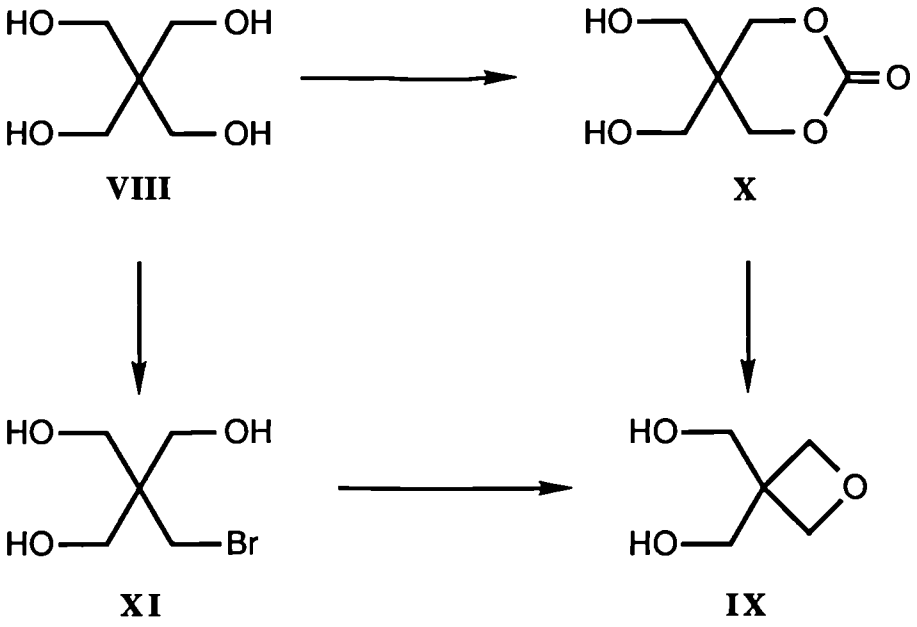


3-Hydroxyoxetane (**V**) underwent reaction with dinitrogen pentaoxide, and the resulting nitrate ester **VI** was polymerised to give poly-3-nitratooxetane (**VII**).



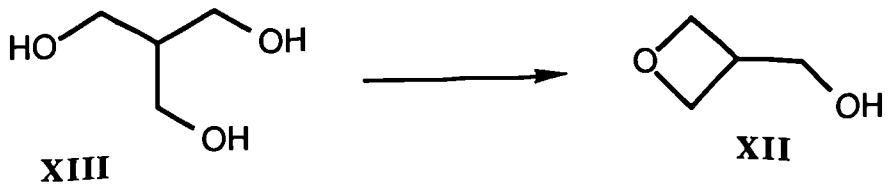
V VI VII

3,3-Bis(hydroxymethyl)oxetane (**IX**) was prepared from pentaerythritol (**VIII**) *via* pyrolysis of the carbonate ester **X**, and by monobromination followed by intramolecular Williamson reaction of the resulting bromohydrin **XI**.



VIII X XI IX

Attempts have been made to synthesise 3-(hydroxymethyl)oxetane (**XII**) by two main routes. The first involved cyclisation of either 2-(hydroxymethyl)propane-1,3-diol (**XIII**) or a protected derivative **XIV** to give either the oxetane **XII** itself or the corresponding derivative **XV**.



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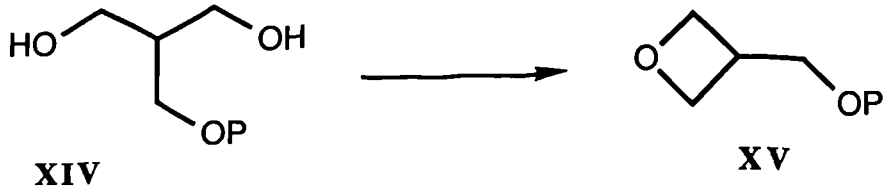
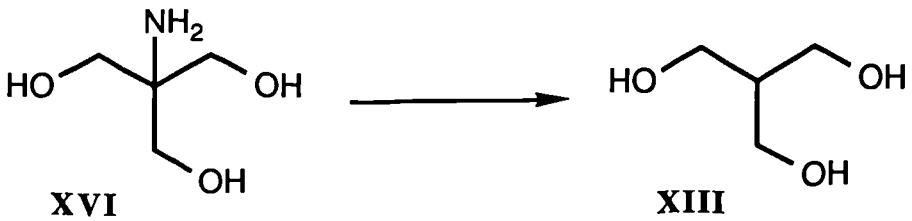


XIV XV

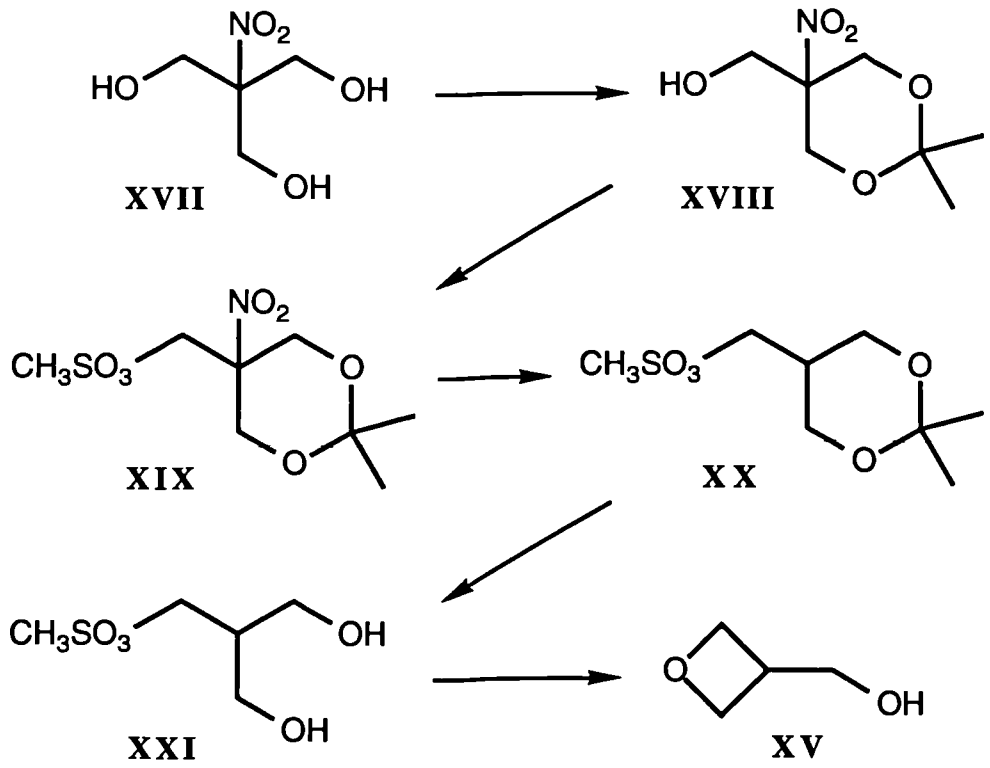
2-(Hydroxymethyl)propane-1,3-diol (**XIII**) was itself prepared by deamination of 2-amino-2-(hydroxymethyl)propane-1,3-diol (**XVI**) using hydroxylamine-*O*-sulphonic acid in base, but it could not be cyclised directly.



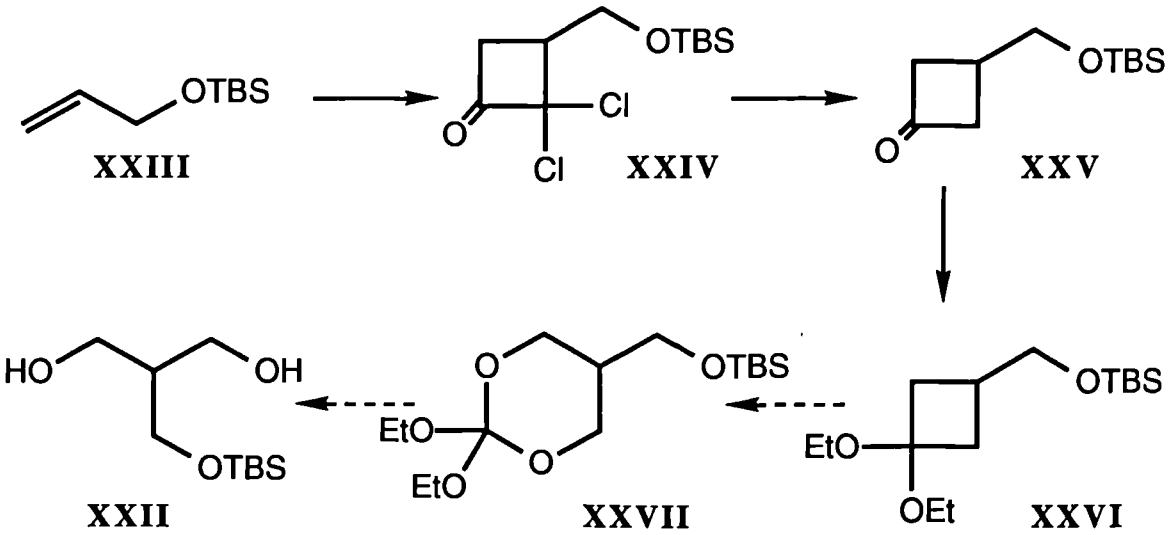
XVI XIII

2,2-Dimethyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane (**XVIII**) was formed by the reaction of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (**XVII**) with 2-methoxypropene. The dioxane **XVIII** was further protected by conversion to 2,2-dimethyl-5-(methanesulphonyloxymethyl)-5-nitro-1,3-dioxane (**XIX**). Hydro-denitration of the nitro-compound **XIX** using tri-*n*-butyltin hydride, yielded 2,2-dimethyl-5-(methanesulphonyloxymethyl)-1,3-dioxane (**XX**), which was hydrolysed to the corresponding diol **XXI**. Treatment of this methanesulphonyl ester **XXI** with strong base afforded 3-(hydroxymethyl)oxetane (**XV**).

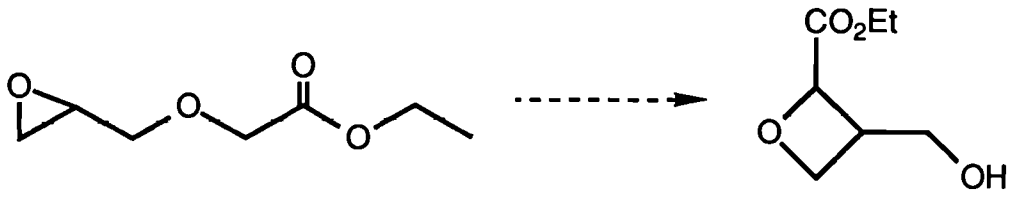
An attempt to form 2-(*t*-butyldimethylsilyloxymethyl)propane-1,3-diol (**XXII**) *via* a five-stage process from allyl *t*-butyldimethylsilyl ether (**XXIII**) was



unsuccessful. Cyclo-addition of the allyl ether **XXIII** with dichloroketene gave 3-(*t*-butyldimethylsilyloxymethyl)-2,2-dichlorocyclobutanone (**XXIV**) which was de-halogenated to give 3-(*t*-butyldimethylsilyloxymethyl)cyclobutanone (**XXV**). This was converted to diethyl acetal **XXVI**, but the acetal failed to undergo Baeyer-Villiger oxidation to 5-(*t*-butyldimethylsilyloxymethyl)-2-oxo-1,3-dioxane (**XXVII**).



A second route to 3-(hydroxymethyl)oxetane (**XII**) involved the formation and attempted cyclisation of the glycidyl ether **XXVIII** to give oxetane **XXIX**. The epoxide **XXVIII** was prepared from ethyl bromoacetate and glycidol, but no cyclisation could be effected.



XXVIII **XXIX**

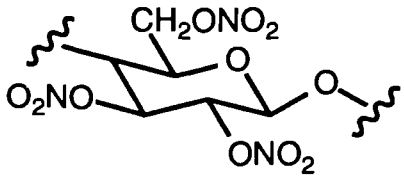
INTRODUCTION

THE USES OF NITRO-COMPOUNDS IN EXPLOSIVES[1, 2]

Nitro-compounds are by far the most common energetic organic components of explosives and propellants. The compounds combine performance and sensitivity and are manufactured at relatively low cost. Four types of nitro-compounds are commonly used in such systems.

1. Nitrate esters[3]

In 1838, Pelouze added cotton to mixed nitric and sulphuric acids and isolated cellulose trinitrate (NC) or 'gun cotton' (**1**).[4] By 1845, Schonbein had shown this nitrate ester to be the first useful alternative to gunpowder. In the following year, Sobrero carried out a similar reaction with glycerine and obtained glyceryl trinitrate or 'nitroglycerine' (NG) (**2**).



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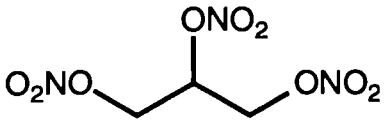

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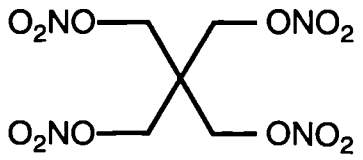
In 1863, Nobel and Nobel founded a small factory for the manufacture of NG, but this was destroyed in an explosion the following year. NG remained of little use due to its unpredictable nature, until 1867 when Alfred Nobel adsorbed it onto kieselguhr and obtained a stabilised system which he named 'dynamite'. This proved superior to any other explosive or propellant. Nobel continued his research, manufacturing firstly 'gelignite', and then 'cordite' from NG by mixing it with NC and, in the case of cordite, with petroleum jelly which suppresses smoke emission. Pentaerythrityl tetranitrate (PETN) (**3**), which is manufactured in a similar manner to NG, was a later

development. PETN found extensive use during World War II as 'pentolite', a mixture of PETN and 2,4,6-trinitrotoluene (TNT) (**4**).

The main disadvantages of the nitrate esters are firstly, the risk of explosion presented by large quantities of such unstable compounds and secondly, their autocatalytic decomposition.



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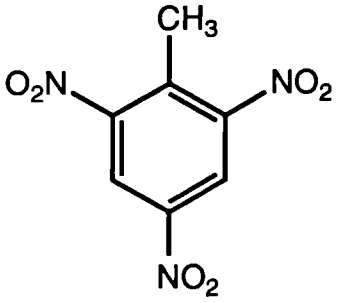

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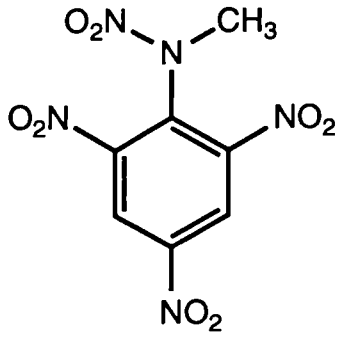
2. Nitramines

The nitramines were developed extensively during World War II. Common nitramines are *N*-methyl-*N*-nitro-2,4,6-trinitroaniline ('Tetryl') (**5**); 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX) (**6**) and 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane (HMX) (**7**). All are high brisance explosives, probably due to their high densities.[5]



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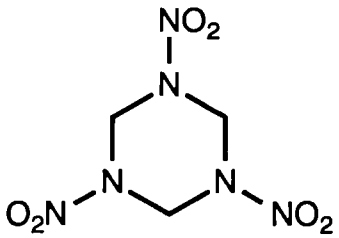

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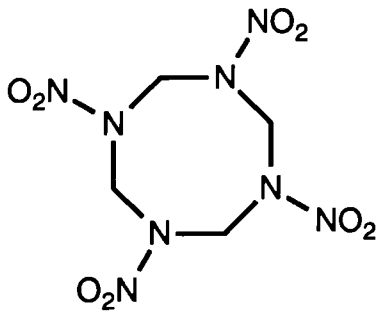

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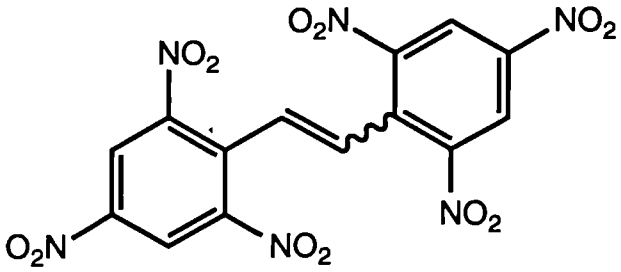
The nitramines are not particularly powerful explosives, and thus are usually used in conjunction with nitroaromatics such as TNT or nitrate esters such as PETN.

N,N-Dinitramines are being developed and although some have proved as powerful as NG, it is unlikely that they will ever find commercial applications due to their greater cost of manufacture .

3. Nitroaromatics

Nitroaromatics such as TNT (**4**) and trinitrobenzene have long been known as explosives. TNT is both cheap and relatively safe to handle, and is still the most widely used military explosive. Current developments in nitroaromatics are directed towards finding systems to withstand the extremes of temperature and pressure associated with space travel.



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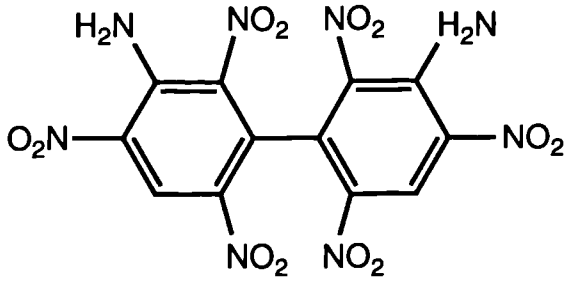

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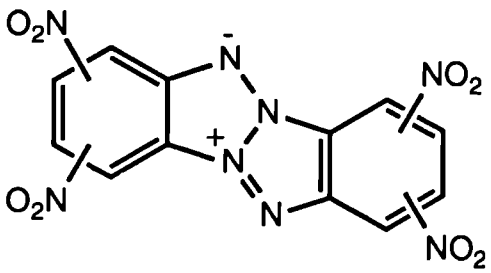

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Compounds such as hexanitrostilbene (**8**), diaminohexanitrobiphenyl (DIPAM) (**9**) and the nitrated dibenzotetraazapentalene (TACOT) **10** have been studied and all are found to have the high melting points and low vapour pressures necessary for use in space applications (*e.g.* the manoeuvring of a satellite), where the propellant may be stored

under extreme conditions for many years before use.

The main disadvantages of the nitroaromatics are that they are relatively low-powered explosives due to their aromatic stability and low hydrogen content, and that they are susceptible to oxidation and attack by alkali.

4. Nitroaliphatics

Nitroaliphatic compounds have the advantage of being simple to prepare and even geminal di- and tri-nitrocompounds are available in good yield. Many of the nitroaliphatics have properties comparable with those of the nitramines. However, the nitroaliphatics are highly sensitive explosives and they also have low thermal stabilities.

The formulation and use of such sensitive systems is hazardous and the nitroaliphatics are not commonly used in explosives or propellants.

ROCKET PROPELLANTS[2]

Rocket propellants are explosives designed to burn smoothly (without the risk of detonation) to provide propulsion energy. Propellants are divided into two types: liquid, and solid.

1. Liquid Propellants

Liquid propellants are further divided into two types: liquid monopropellants and liquid bipropellants. Liquid monopropellants consist of a single material which is capable of spontaneous decomposition to gaseous products. The most useful monopropellant is hydrazine, which decomposes on an iridium catalyst to give ammonia, hydrogen and nitrogen gases. Liquid bipropellants consist of the fuel and an oxidiser. The two components are pumped into a combustion chamber where they decompose either by their own reaction (hypergolic) or by ignition (non-hypergolic). Two common bipropellant systems are dimethylhydrazine - nitric acid, a hypergolic system and liquid

hydrogen - liquid oxygen, a non-hypergolic system.

The main disadvantage of the liquid propellants is the complex plumbing and control needed to ensure a smooth reaction.

2. Solid Propellants

Solid rocket motors are much simpler because the whole charge is already inside the combustion chamber and combustion takes place on the surface of the solid. The rate of combustion is controlled by the shape of the charge (grain). A solid, cigarette-shaped grain may be used for slow burning, or a more complicated grain with geometrical channels running through it may be used for much faster combustion. In an extreme case, some shoulder launched rocket motors must be all burnt on launch (ABOL) to protect the operator from the hot exhaust gases as the missile leaves its launcher. Clearly, since the surface area controls the rate of combustion, the mechanical properties of the propellant are of paramount importance.

Solid propellants can be divided into three categories, double-base, modified double-base and composite. Double base propellants are similar to Cordite, in that they consist of nitroglycerine and nitrocellulose as a rigid colloidal mixture which can either be cast or extruded to give the required grain. Modified double-base propellants contain aluminium powder and an oxidant (usually ammonium perchlorate) to increase the power of the propellant.

(a) Composite Propellants

Composites differ from the other types of solid propellant in that they do not contain a recognised explosive such as nitroglycerine. The use of a mixture of oxidant and fuel causes no loss of power in the propellant, unlike in an explosive charge where the combustion needs to be extremely rapid. Composite propellants are divided into two types, those made with polymers which although solid at room temperature may be

poured at higher temperatures (plastic composites), and those made with polymers which are cross-linked on final polymerisation and do not flow on heating (rubbery or elastic composites).

Although the polymer (binder) only accounts for 10-15% of the weight of the charge, it is largely responsible for the mechanical properties of the material. The most important mechanical properties are high tensile and compressive strengths and good elasticity. In a rocket, the grain is usually bonded to the combustion chamber wall (case-bonded), and whatever extremes of temperature are incurred, the case-bonding must not be lost. Loss of case-bonding or any cracking of the grain allows the flame front to expand, and since rocket motors are designed only for low pressure operation (15-30 MPa), this can result in an explosion.

The oxidiser accounts for up to 85% of the mass of the charge and is usually ammonium perchlorate. A metal cation would take up oxygen and give solid products. As with double-base propellants, aluminium may be added to composite propellants to great effect.

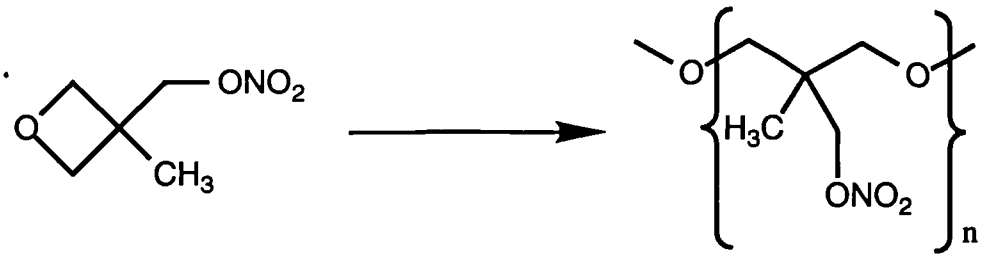
Plastic composites were the first of the composite propellants and consist mainly of polystyrene, polyvinylchloide or polyisobutene. The latter became the material of choice for composites. Although 90% is the optimum ammonium perchlorate loading, only 85% is used due to poor mechanical properties at higher loadings. The solid components are simply mixed with the molten polymer and extruded or cast into the rocket casing. The main problem with plastic composites is their poor stress resistance at low temperatures.

The first rubbery composites were polyurethanes which were mixed with the oxidant and cross-linking agent before being allowed to cure at elevated temperatures for several weeks. Most modern elastic composites are based on hydroxyl terminated polybutadiene (HTPB) cross-linked with diisocyanate, or on carbonyl terminated polybutadiene (CTPB) cross-linked with an epoxide or with an aziridine. The HTPB and CTPB systems have excellent mechanical properties and case-bond very well.

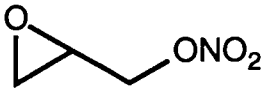
(b) Energetic Binders

Clearly, the use of an energetic polymer instead of an inert polybutadiene is advantageous, as this allows an improved oxygen balance at lower oxidiser loadings. One such system is poly-3-(nitratomethyl)-3-methyloxetane (polyNIMMO) (**12**),[6] which is prepared by cationic ring opening polymerisation of the readily available 3-(nitratomethyl)-3-methyloxetane (NIMMO) (**11**). The product is moderately energetic, and whilst its glass transition temperature (Tg) is too high at -35°C for it to be of much practical use in this form, the material can be plasticised with glycidyl nitrate (**13**) to good effect.

A random co-polymer of NIMMO (**11**) and glycidyl nitrate (**13**) in equal amounts is significantly more energetic, and has a much improved Tg of -48°C.



11 **12**



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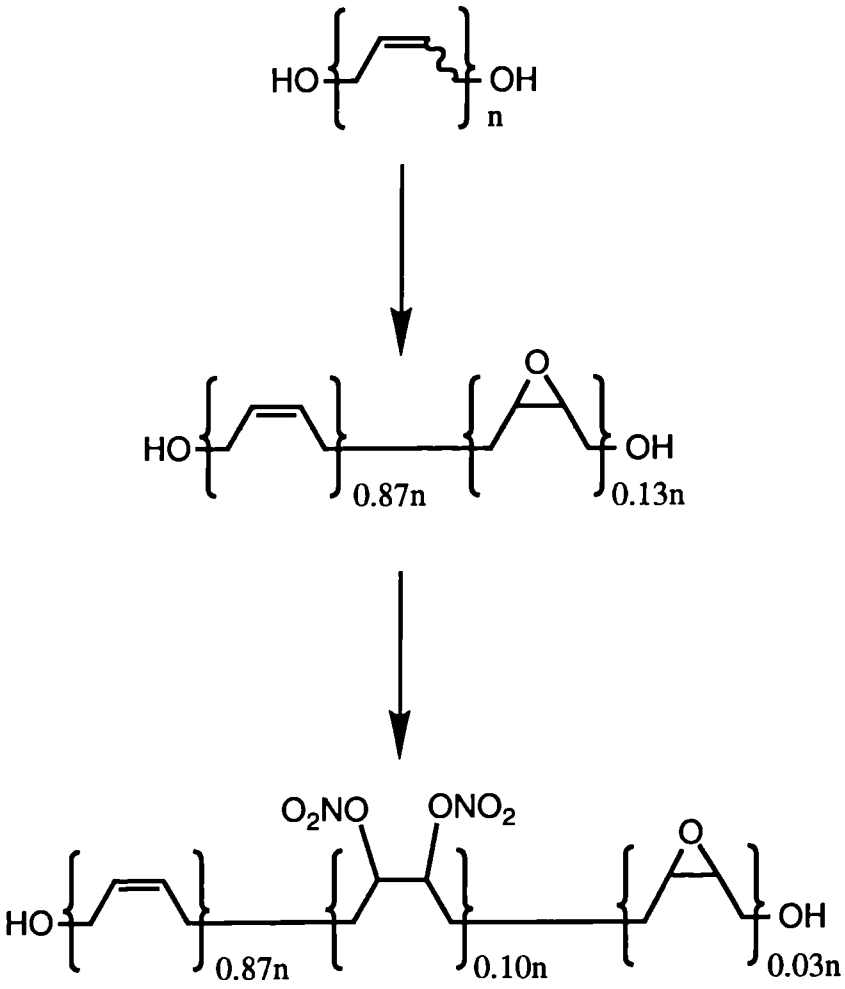
A second, and less expensive approach to energetic binder systems involves the epoxidation and nitration of an HTBD polymer (see Scheme 1). In order to retain good mechanical properties and a Tg < -50°C, only 10-15% of the double bonds were oxidised and the product was treated with dinitrogen pentoxide to give the *vic* dinitrate ester. This material is again only moderately energetic but can be energised by using energetic plasticisers.

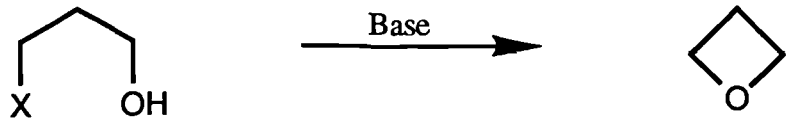


Scheme 1

THE SYNTHESIS OF 3-SUBSTITUTED OXETANES

1. The Intramolecular Williamson Reaction

The intramolecular Williamson reaction is the most commonly used reaction for the preparation of oxetanes.[7]



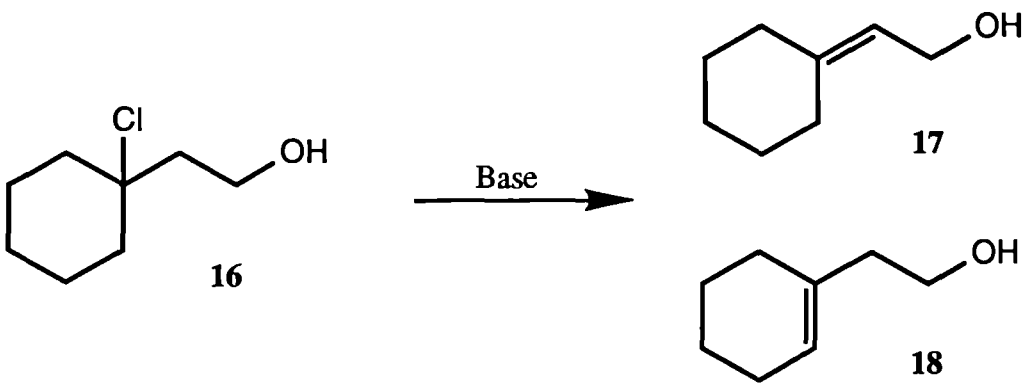
14 **15**

Treating a 1,3-halohydrin **14** with base gives the corresponding oxetane **15** by deprotonation followed by intramolecular nucleophilic substitution. In general, the reaction proceeds much more slowly than the corresponding oxirane formation.[8] This slow rate of reaction often allows the competing reactions, conjugate elimination and intermolecular nucleophilic substitution, to consume much of the starting material.[9]

(a) Substituent Effects

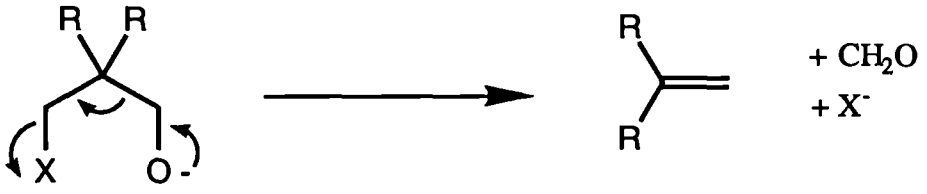
Alkyl substituents on a 1,3-halohydrin can greatly effect the yield of oxetane obtained from a Williamson reaction. Unlike the corresponding oxirane formation, where adding alkyl substituents to a 1,2-halohydrin invariably increases the yield of oxirane,[10] the yield of oxetane can either be increased or decreased by altering the substitution pattern.

Substitution at the halogen bearing carbon atom greatly decreases the yield of oxetane. The addition of alkyl groups greatly stabilises the carbocation intermediate needed for a unimolecular elimination to take place. Tertiary halides give no oxetane at all. Thus, treating 1-chloro-(2-hydroxyethyl)cyclohexane (**16**) with base gave only the two isomeric, unsaturated alcohols **17+18**.[11]



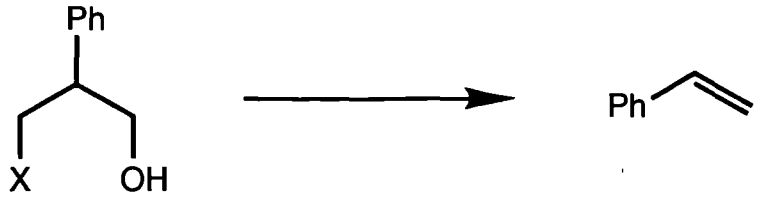
16 17 18

Substitution at the central carbon atom of the halohydrin also causes a marked reduction in the yield of oxetane.



19 20

The γ-haloalkoxide ion **19** can undergo a conjugate elimination to give alkene **20**, halide ion and formaldehyde. The yield of oxetane decreases with an increase in the thermodynamic stability of the alkene byproduct. In the case of an extremely stabilising 2-aryl substituent, no oxetane is obtained at all. Thus, 2-phenyl-1,3-halohydrins **21** yield only styrene when treated with base.[12]



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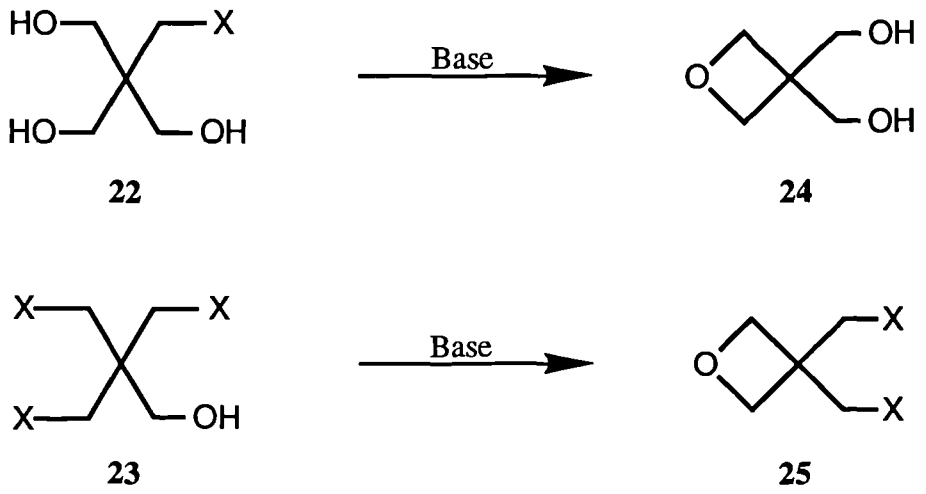
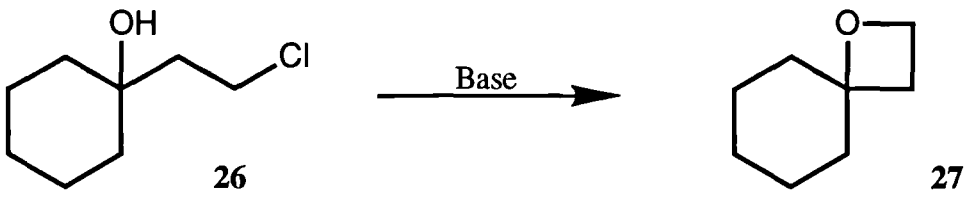
Two exceptions to the above rule are known. When treated with base, the

2,2-bis(hydroxymethyl)-3-halopropan-1-ols[13] **22** and 2,2-bis(halomethyl)-3-haloprop-an-1-ols[14] **23** gave excellent yields of 3,3-bis(hydroxymethyl)oxetane (**24**) and 3,3-bis(halomethyl)oxetane **25** respectively. This is probably due to the enforced proximity of the reacting functional groups.

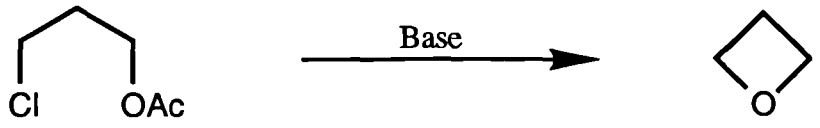


Alkyl substitution at the carbinol increases the yield of oxetane by enhancing the nucleophilicity of the alkoxide ion. Thus, 1-(2-chloroethyl)cyclohexanol (**26**) gave a good yield of 1-oxaspiro[3.5]nonane (**27**) when treated with base.[9] This result is in clear contrast to the 1,2-elimination when 1-chloro-(2-hydroxyethyl)cyclohexane (**16**) was treated with base (see p. 10).



(b) The Use of Esters

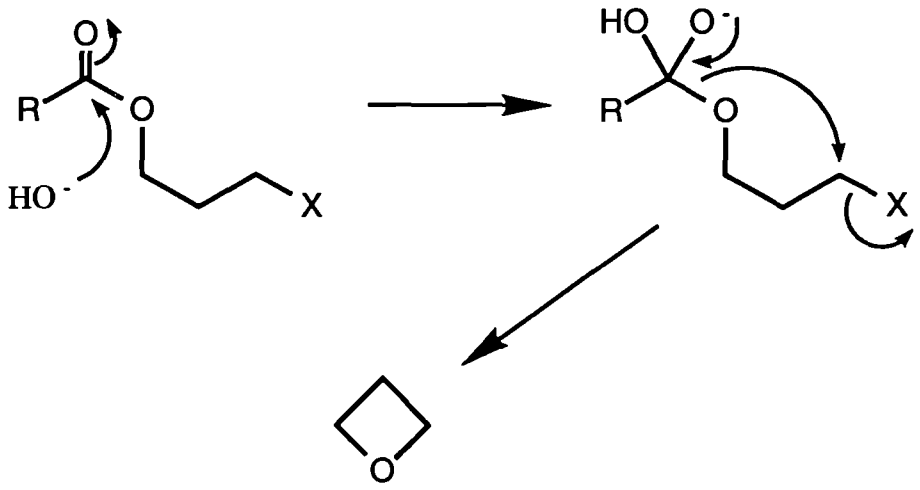
In most cases the esterification of a 1,3-halohydrin increases the yield of oxetane obtained from the Williamson reaction. The yield of oxetane **15** was increased from 25 to 45% by using 3-chloropropyl acetate (**28**) rather than halohydrin **14**.[14]



28 **15**

An exception to the above rule are the 2,2-dialkyl-1,3-halo-esters which offer no improvement in yield over the parent alcohols.

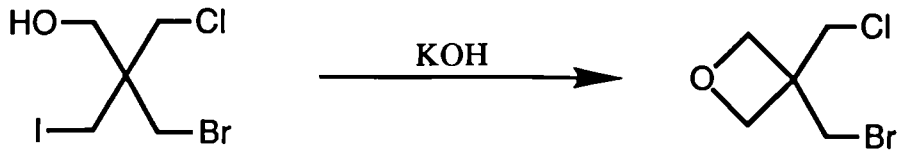
The mechanism of the reaction is unknown but the following scheme has been proposed.[7]



Scheme 2

(c) Leaving Group Effects

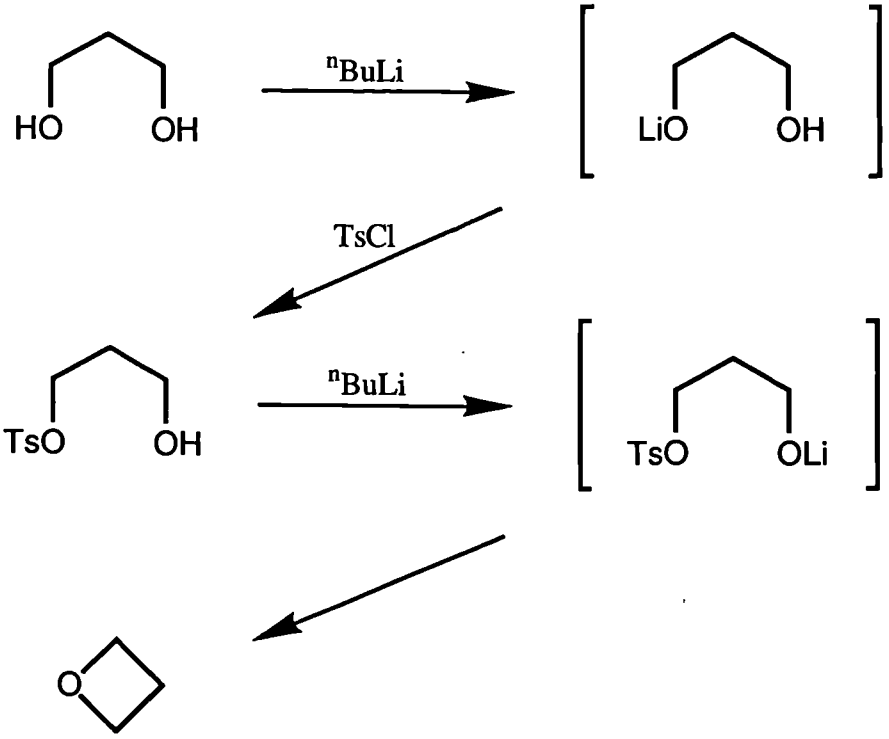
Chloro-compounds are most commonly used for oxetane formation. This is due to their relative inexpense and ease of formation. Bromo-compounds give slightly better yields but are much rarer and the 1,3-iodohydrins are rarely used at all. As would be expected, the most weakly bound halogen is displaced first. The cyclisation of 2-(bromomethyl)-2-(chloromethyl)-3-iodopropan-1-ol (**29**) with potassium hydroxide gave 3-(bromomethyl)-3-(chloromethyl)oxetane (**30**) in 65% yield.[14, 17]



29 **30**

Mono-alkyl and arylsulphonates of 1,3-diols have been used in Williamson reactions and were found to give particularly good results with potassium *t*-butoxide as the base.[17] The main problem with this reaction is the difficulty with which the mono-tosylates are prepared although this can be overcome by using the ditosylate and cyclising with hot potassium hydroxide.[18] This reaction, which proceeds *via* the monotosylate, also has the advantage of giving less conjugate elimination than the bromohydrin.

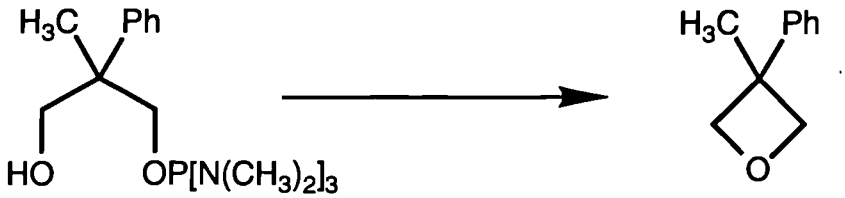
One effective method of preparing the monotosylate of a diol has been reported (see Scheme 3).[19]



Scheme 3

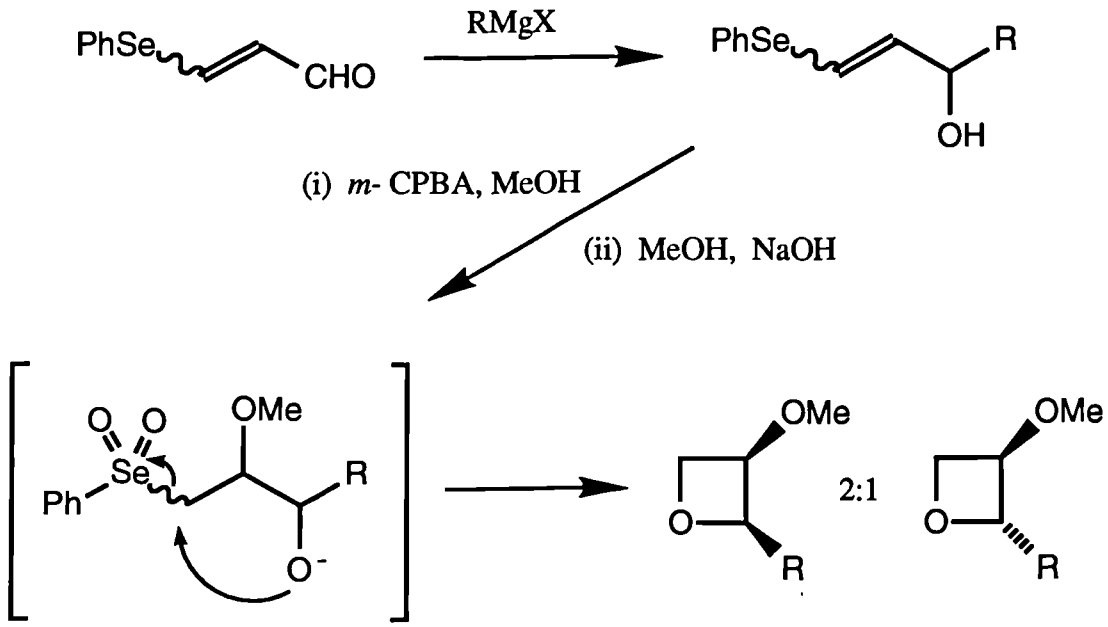
Deprotonation of the diol with *n*-butyllithium, followed by quenching of the anion with tosyl chloride gives the monotosylate. The addition of a second equivalent of *n*-butyllithium gives the oxetane in good yield.

A further improvement in the yield of 3,3-disubstituted oxetanes was obtained by the use of tris(dimethylamino)phosphine oxide as the leaving group.[20] Thus, 3-methyl-3-phenyloxetane (**31**) was prepared from phosphonium salt **32** in 70% yield.



32 **31**

3-Aryloxetanes are not available from the pyrolysis of carbonate esters, normally the method of choice for the synthesis of 3,3-substituted oxetanes.



Scheme 4

Selenium leaving groups have been employed in a general route to 3-methoxy-oxetanes from 3-(phenylseleno)propenal (see Scheme 4).[21] Grignard addition followed by oxidation with *m*-chloroperoxybenzoic acid and addition of methanol, gave a product which cyclised in base to give a mixture containing mainly the *cis*-2,3-disubstituted oxetane.

Many other leaving groups have been employed but none gave consistently good results.

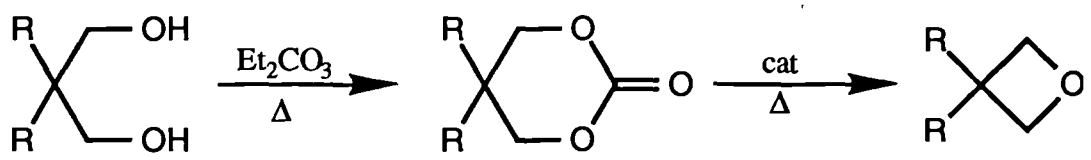
(d) The Choice of Base

As expected for an S_N2 reaction, the best yield of oxetane is achieved using a strong base in a solvent of low polarity. Concentrated aqueous, powdered or ethanolic potassium hydroxide all give good results with 1,3-halohydrins. Weaker, aqueous bases give greater yields of elimination products.[12]

Two other systems which give particularly good results are potassium *t*-butoxide in *t*-butanol with mono-arenesulphonate esters,[17] and sodium methoxide in methanol with tris(dimethylamino)phosphonium chloride salts.[20]

2. The Pyrolysis of Carbonate Esters

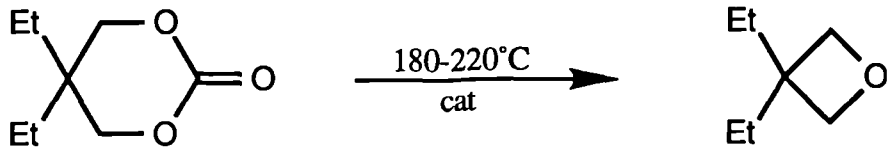
The synthesis and subsequent pyrolysis of the carbonate esters of 1,3-diols is the method of choice for the synthesis of 3,3-dialkyloxetanes **35**. The carbonate esters (**34**) are formed in a simple base catalysed transesterification of diethyl carbonate or ethylene carbonate with a 2,2-dialkyl-1,3-diol **33**.[22]



33 **34** **35**

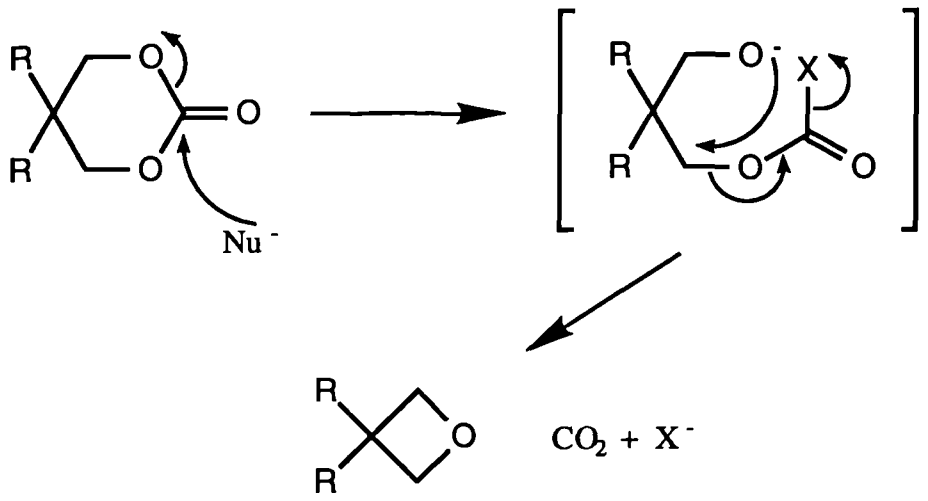
Pyrolysis of the crude carbonate ester is carried out between 180 and 350°C depending on the nature of the substituents and on the catalyst employed.

Searles[23] reported the decomposition of 5,5-diethyl-1,3-dioxan-2-one (**36**) to give 3,3-diethyloxetane (**37**) at 180-220°C using copper (II) carbonate - copper (II) hydroxide catalyst, and the same reaction at 350°C using alumina as the catalyst.



36 **37**

The pyrolysis is thought to proceed *via* nucleophilic attack by the catalyst on the carbonyl group, causing an intramolecular Williamson type reaction (see Scheme 5).

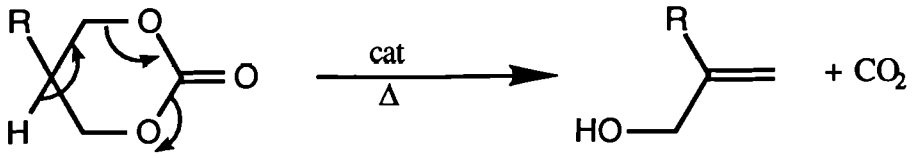


Scheme 5

Many bases have been used to catalyse the pyrolysis step.[23] Potassium cyanide and potassium carbonate gave the best results but alumina, copper (II) carbonate - copper (II) hydroxide, sodium cyanide, sodium carbonate, silver carbonate, potassium

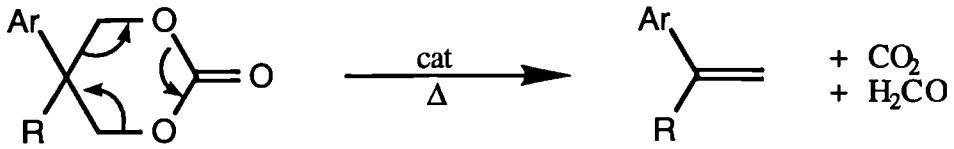
propionoate, potassium acetate, magnesium oxide, calcium oxide, sodium methoxide, potassium hydroxide, potassium *t*-butoxide, sodium ethoxide, sodium metal, ammonia, diethylamine and lithium amide have all been used.

Pyrolyses using carbonates **38**, with at least one β-proton, give decomposition in the manner first reported by Carothers[24] in 1920, to give the allylic alcohols **39**.



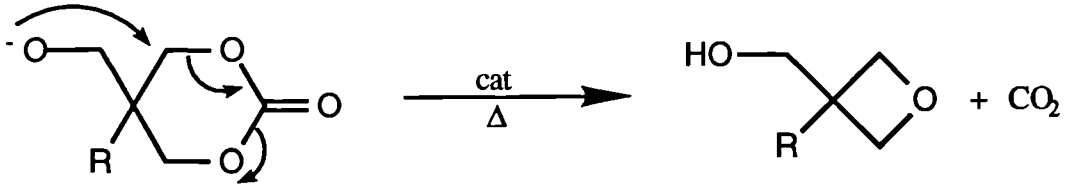
38 **39**

A similar problem prevents the formation of 3-aryloxetanes from the carbonate esters **40** by this method. The high stability of the resulting styrenes **41** drives a conjugate elimination of carbon dioxide and formaldehyde.



40 **41**

Carbonate esters **42**, with free β-hydroxymethyl substituents, decompose smoothly at particularly low temperatures often without a catalyst, to give 3-(hydroxymethyl)oxetanes **43**. This decomposition probably involves intramolecular nucleophilic attack by the hydroxyl oxygen.

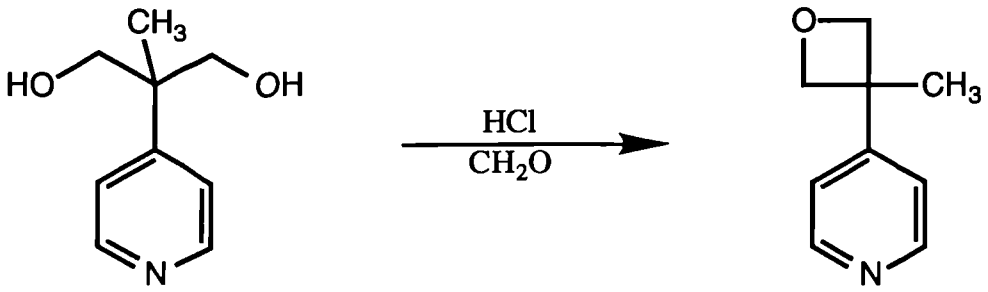


42 **43**

It should be noted that in all of the above reactions, the carbonate ester is probably present as an equilibrium mixture of cyclic and open chain forms, but both systems are believed to undergo identical reactions.

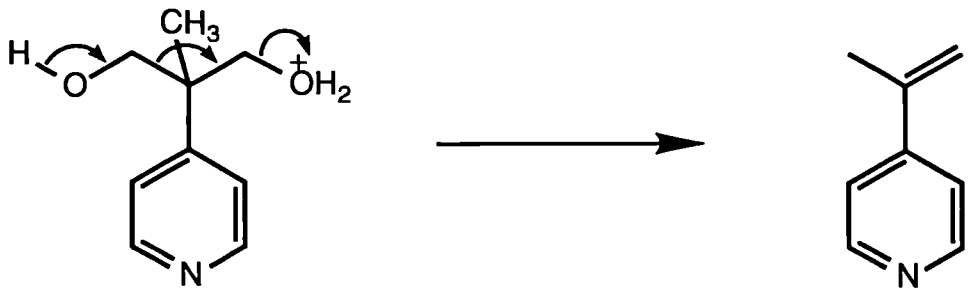
3. The Cyclodehydration of 1,3-Diols

The cyclodehydration of 1,3-diols using strong acids is not a general reaction. However, 2-methyl-2-(4-pyridyl)-1,3-propanediol (**44**) was converted to 3-methyl-3-(4-pyridyl)oxetane (**45**),[25,26] using hydrochloric acid in the presence of formaldehyde.



44 **45**

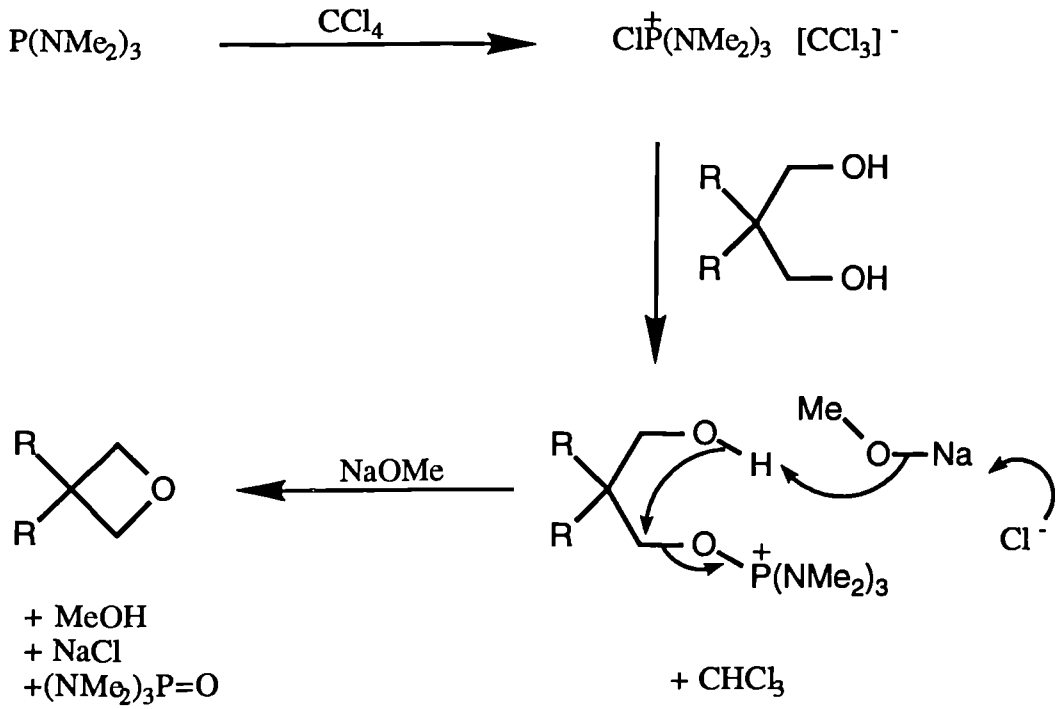
Formaldehyde was added to supress the conjugate elimination of formaldehyde and water, which would yield 2-(4-pyridyl)propene (**46**).



46

Castro[20] reported yields of 3,3-dialkyloxetanes up to 70% when 2,2-dialkyl-propane-1,3-diols were treated with tris(dimethylamino)phosphine and carbon tetra-

chloride followed by sodium methoxide (see Scheme 6).

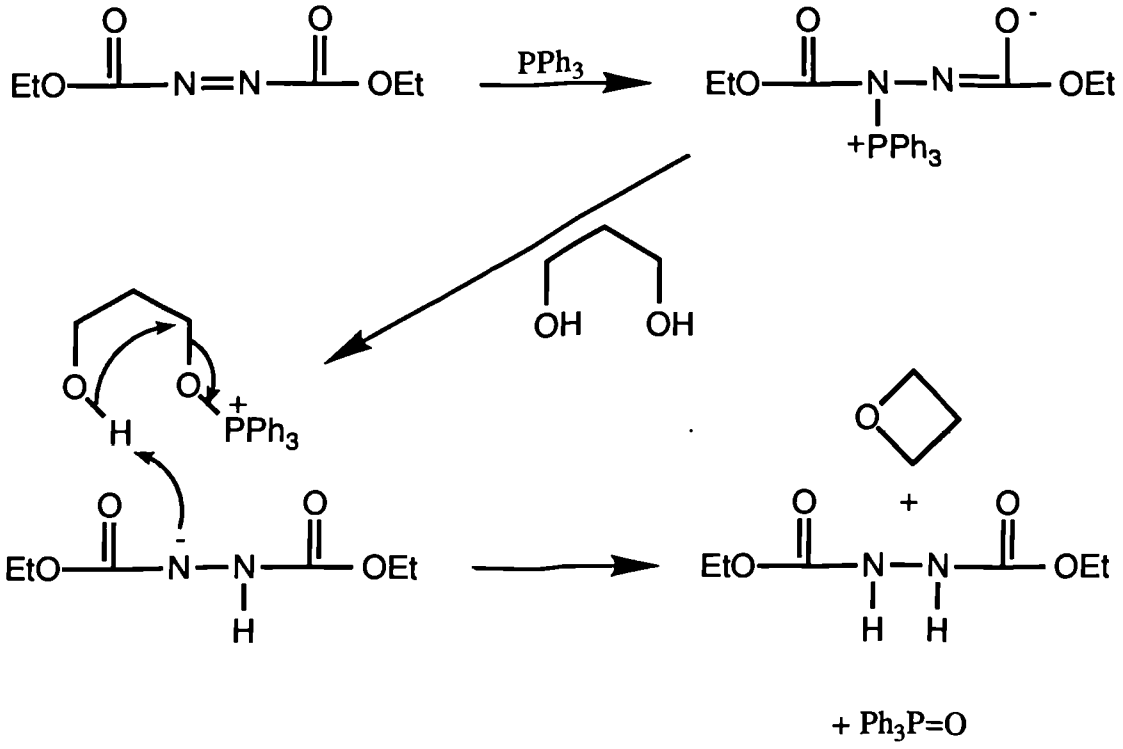


Scheme 6

The reaction proceeds equally well with 2-aryl-1,3-diols, and good yields were obtained even for strained systems such as 1,1-bis(hydroxymethyl)cyclobutane (**47**) which gave 2-oxaspiro[3.3]heptane (**48**).

47 **48**

More recently, the quantitative cyclisation of α,ω-diols was reported by Carlock.[27] The diol was added to diethyl azodicarboxylate and triphenyl phosphine, and cyclised instantly at room temperature (see Scheme 7).

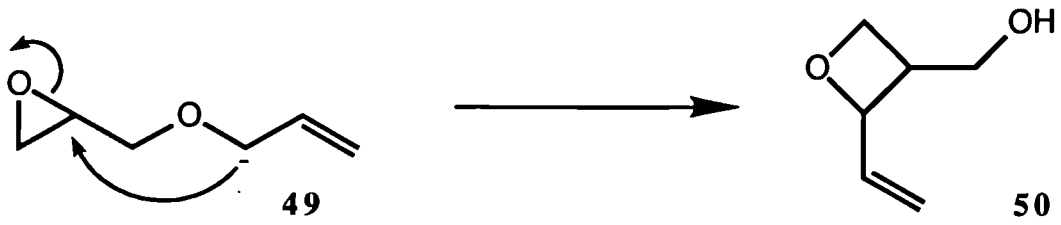


Scheme 7

The yield of oxetane was 98%, whilst oxirane and tetrahydrofuran were each obtained in 100% yield from similar reactions.

4. The Cyclisation of Allyl Glycidyl Ethers

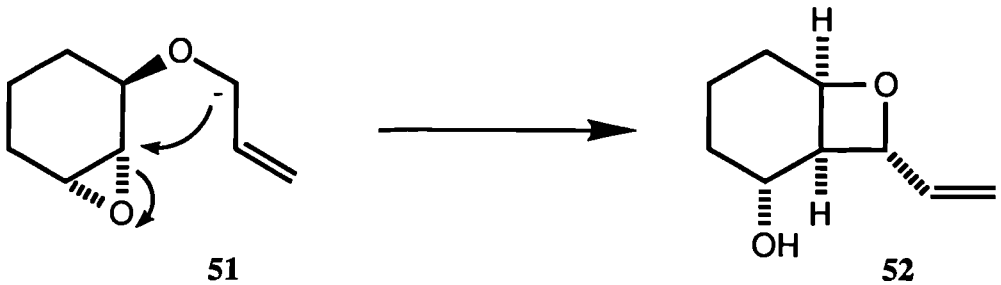
The deprotonation of allyl glycidyl ethers **49** has been found to give the 2-vinyloxetanes **50**.



49 **50**

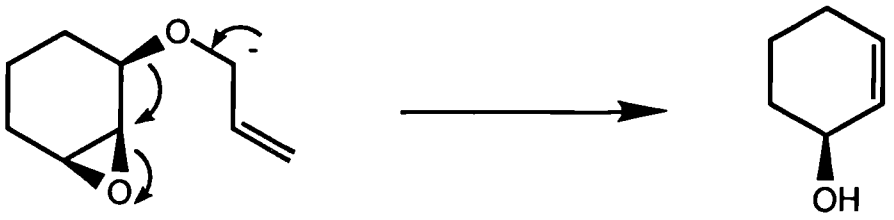
Still[28] reported an excellent yield of the bicyclic oxetane **52** on treating the *trans*-epoxy allylic ether **51** with *sec*-butyllithium in tetrahydrofuran containing 4%

hexamethylphosphoramide (HMPA) at -17°C.



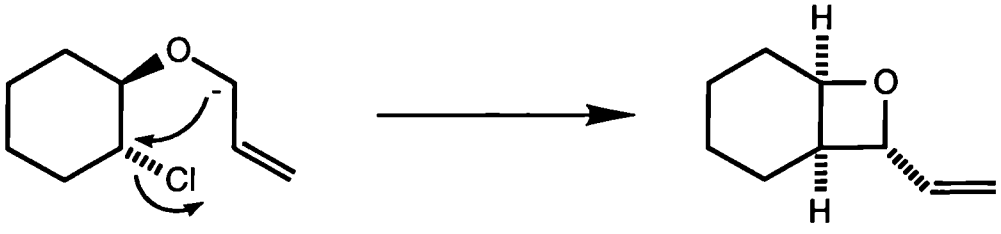
51 52

The reaction exhibits both high regioselectivity and high stereoselectivity. Clearly the same reaction with the *cis*-epoxy allylic ether **53** would be impossible for steric reasons. This reaction instead gave the allylic alcohol **54**.



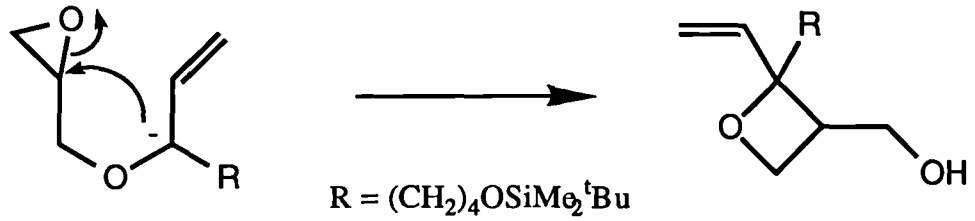
53 54

Similar results were obtained with *trans*-2-allyloxycyclohexyl chloride (**55**) which gives a good yield of oxetane **56** under the same reaction conditions.

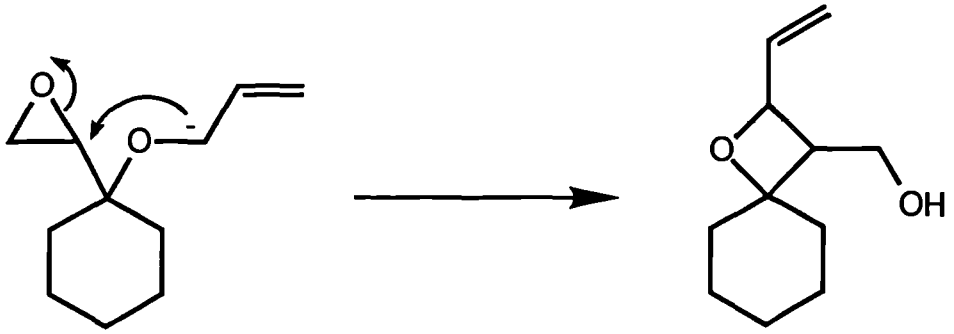


55 56

Bird[29] reported good yields of the highly substituted oxetanes **58+60** from allyl glycidyl ethers **57+59** using similar conditions.

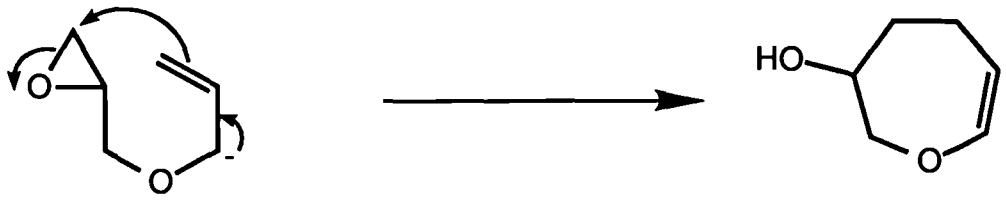


57 58



59 60

However, simpler systems such as allyl glycidyl ether (**61**) itself were found to give predominantly tetrahydro-oxepanols **62**.



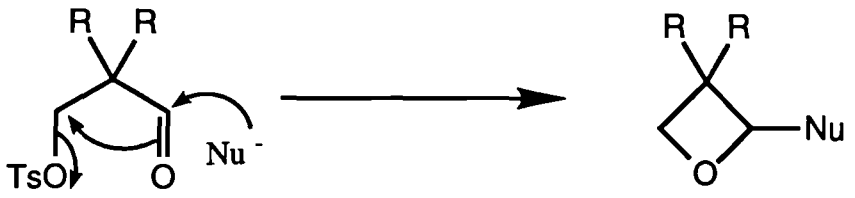
61 62

5. Other Methods

Most carbonyl compounds undergo photochemical [2+2] cyclisations with alkenes to give oxetanes. One notable exception to this, is formaldehyde. Thus, oxetanes unsubstituted in the 2-position are not available from this reaction.

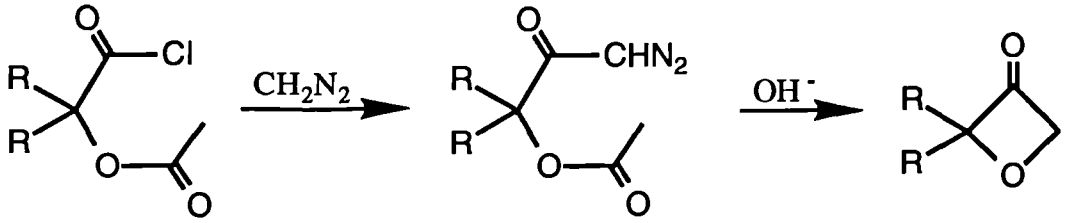
The cyclisation of carbonyl compounds with good leaving groups in the β-position has received much attention in the literature. Nerdel and co-workers[30, 31, 32] prepared many 2,3,3-trisubstituted systems **64** by the action of a variety of nucleophiles

on β-tosyloxyaldehydes **63**.



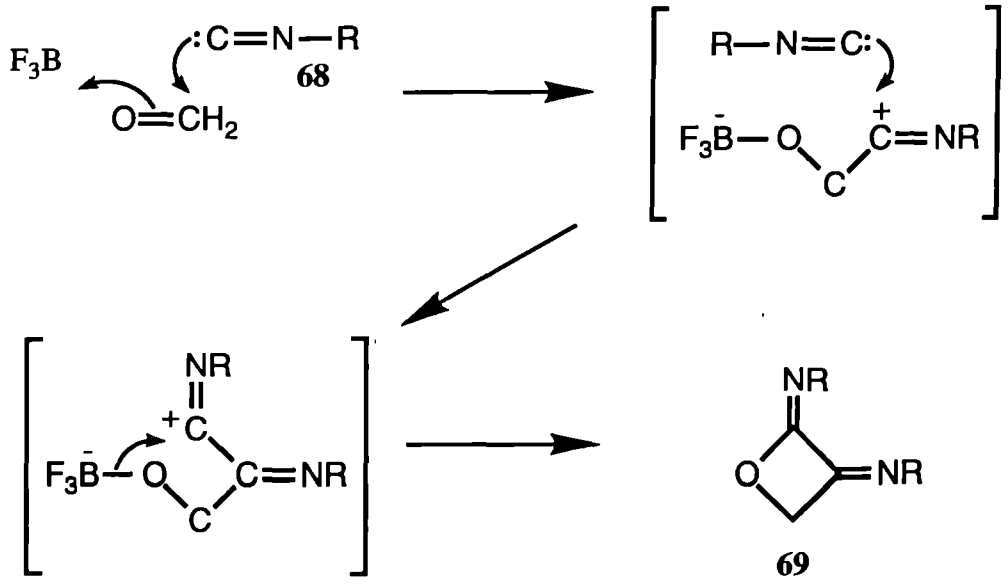
63 **64**

3-Oxetanones **67** have been prepared in very low yields from acetoxyacetyl chlorides **65** by treating with diazomethane, and subsequent treatment of the resulting diazocompound **66** with base.[33]



65 **66** **67**

Kabbe[34] obtained 2,3-bis(alkylimino)oxetanes **69** from formaldehyde and two equivalents of an isonitrile **68** using boron trifluoride catalysis.



69

THE REACTIONS OF OXETANES

1. Reactions with Electrophiles

The oxygen atom of an oxetane ring possesses an exceptionally high electron donor ability. This causes the oxetane ring to interact with most electrophiles.[35] Such interactions form the most important group of reactions undergone by oxetanes.

The electrophilic interactions are of two types. Weak electrophiles react with oxetanes to form adducts for which equilibrium data can be measured. Stronger electrophiles bond irreversibly to the oxygen atom and result in ring-cleavage.

(a) Reactions with Weak Electrophiles

Oxetanes form hydrogen bonds with alcohols, in a manner similar to other ethers. Oxetanes also form charge-transfer complexes with iodine. In both cases, the electron donor ability of the oxetane is found to vary according to its substitution pattern.[36] Thus, 2,2-dialkyloxetanes show an enhanced electron donor ability, whilst 3,3-dialkyloxetanes show a reduced ability. This seems to indicate that the electron donor ability of the oxetane is dependent on steric factors, and that the observed trend results from changes in the oxetane structure, caused by the addition of substituents.

In addition to hydrates[38] and iodine complexes,[39] oxetane itself forms adducts with dinitrogen tetraoxide.[40]

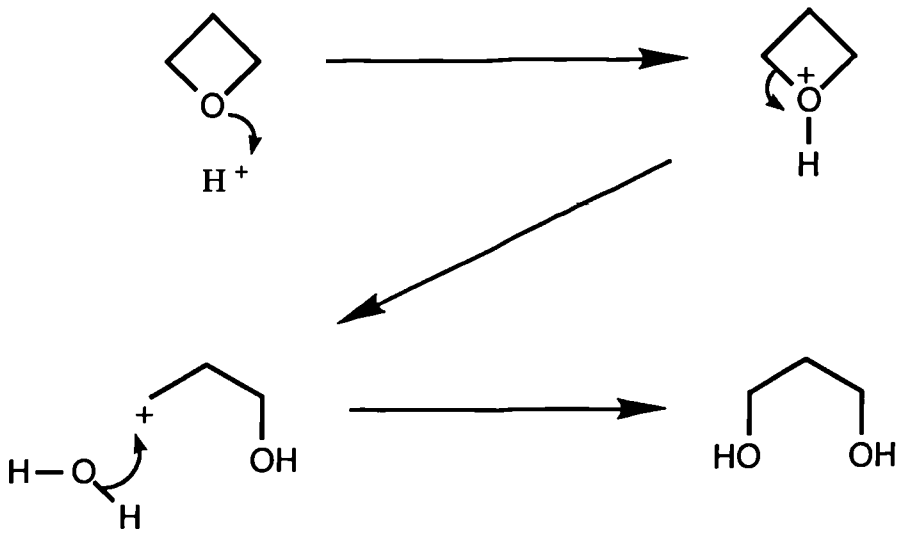
(b) Reactions with Stronger Electrophiles

The complexing of a stronger electrophile with the ring oxygen atom causes a weakening of the ring carbon - oxygen bonds, promoting both spontaneous bond fission and nucleophilic attack at the α-carbon atoms.

In dilute sulphuric acid for example, oxetanes are hydrolysed to give 1,3-glycols.[41] The reaction proceeds *via* protonation of the ring oxygen, followed by ring-

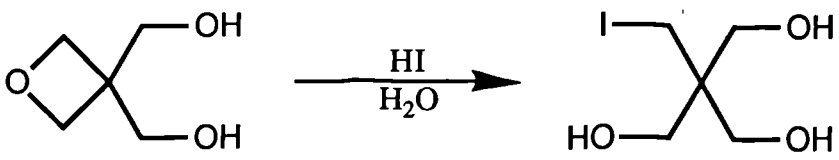
opening and attack of the resulting carbocation by a water molecule (see Scheme 8).

Similar reactions with other mineral acids give products resulting from nucleophilic attack by the conjugate base.

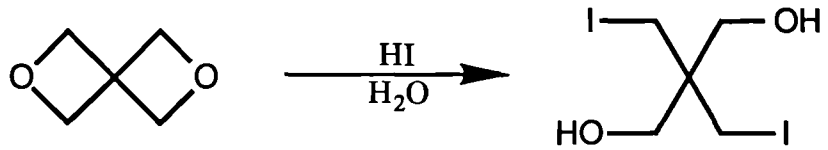


Scheme 8

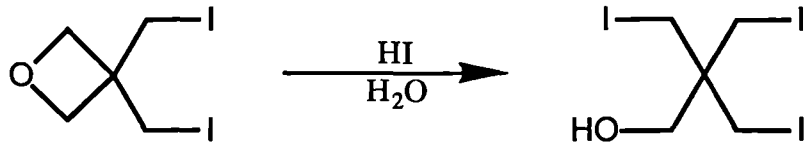
Thus, hydrochloric, hydrobromic and hydriodic acids all give the corresponding 1,3-halohydrins. This reaction has been used to make many halohydrins and is especially useful for the preparation of the pentaerythrityl halides. Thus, 2-(hydroxymethyl)-2-(iodomethyl)propane-1,3-diol (**71**), 2,2-bis(iodomethyl)propane-1,3-diol (**73**) and 3-iodo-2,2-bis(iodomethyl)propan-1-ol (**75**) were prepared from 3,3-bis(hydroxymethyl)oxetane (**70**),[13] 2,6-dioxaspiro[3.3]heptane (**72**)[42] and 3,3-bis(iodomethyl)oxetane (**74**)[14] respectively, by treating the oxetane with aqueous hydriodic acid.



70 **71**

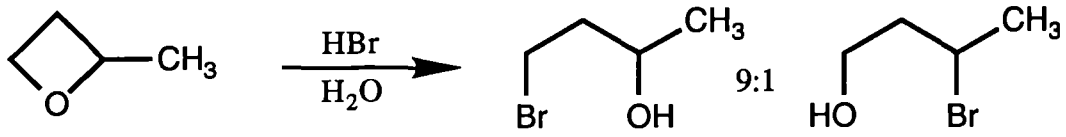


72 **73**



74 **75**

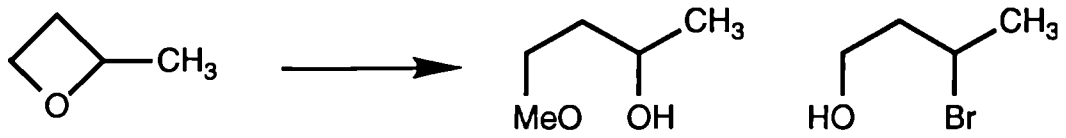
Unsymmetrical oxetanes react with mineral acids to give mixtures of ring-opened products. The predominant product is that corresponding to the ring-opening of the oxetane by cleavage of the bond between oxygen and the least substituted α-carbon atom. Thus, 2-methyloxetane (**76**) gave a mixture of 4-bromobutan-2-ol (**77**) and 3-bromobutan-1-ol (**78**) in a ratio of 9:1.[43]



76 **77** **78**

Clearly this is not an S_N1 reaction as was the sulphuric acid catalysed hydrolysis (Scheme 8), since that would be expected to give predominantly the product resulting from the formation of a secondary carbocation, *i.e.* 3-bromobutan-1-ol (**78**). This reaction gives mainly the product resulting from S_N2 attack of the bromide ion at the least hindered α-carbon atom, but by varying the nucleophile employed, it can be shown that such reactions lie on the S_N1 / S_N2 mechanistic borderline.

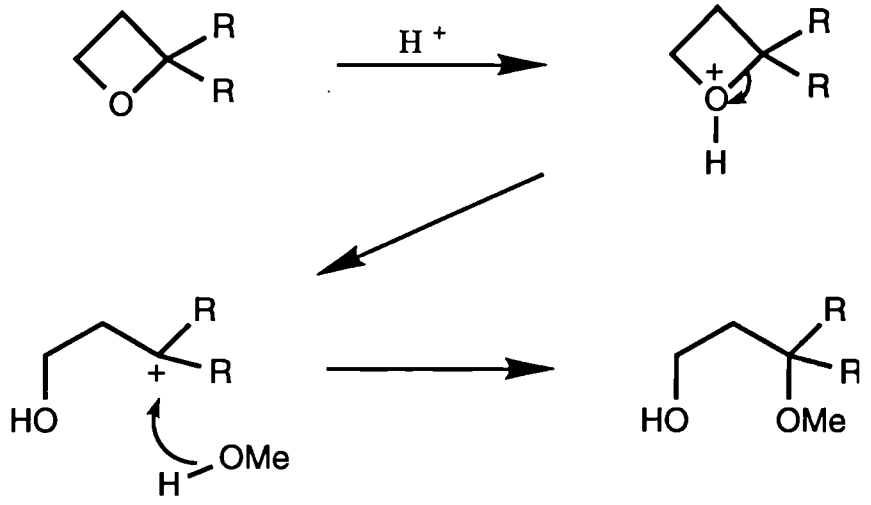
Acid-catalysed methanolysis of oxetanes gives similar results. Thus, treatment of 2-methyloxetane (**76**) with perchloric acid in methanol gave a mixture of 4-methoxy-butan-2-ol (**79**) and 3-methoxybutan-1-ol (**80**) in which the former predominated.[44]



76 **79** **80**

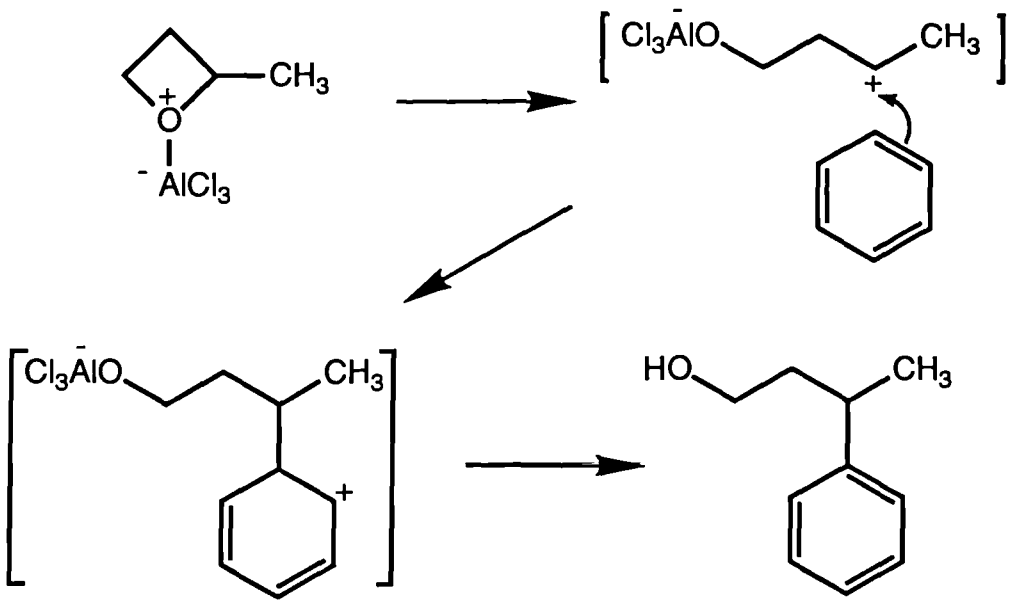
By varying the solvent used, the reaction was shown to be on the mechanistic borderline.

The acid catalysed solvolysis of 2,2-dialkyloxetanes occurs *via* an S_N1 type mechanism. This gives 3-substituted 3-methylbutan-1-ols, the reaction obviously being directed by the stability of a tertiary carbocation (see Scheme 8a).



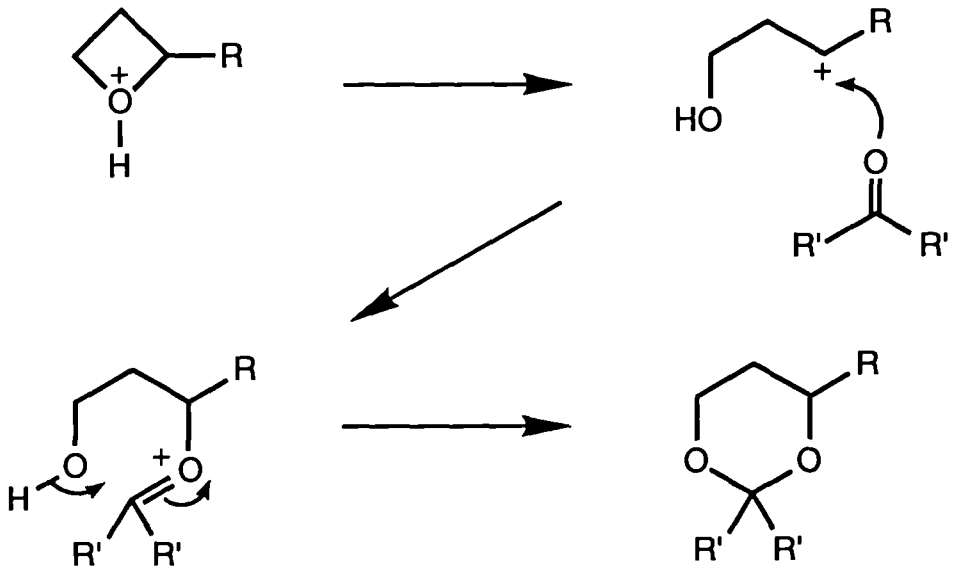
Scheme 8a

[1] Oxetanes can be employed in Friedel-Crafts type alkylation reactions. Thus, 2-methyloxetane in the presence of aluminium (III) chloride can be used to alkylate an aromatic nucleus. The reaction proceeds *via* an S_N1 ring-opening mechanism of the oxetane to give the product resulting from attack of the aromatic ring at the most substituted α-carbon atom of the oxetane (see Scheme 9).



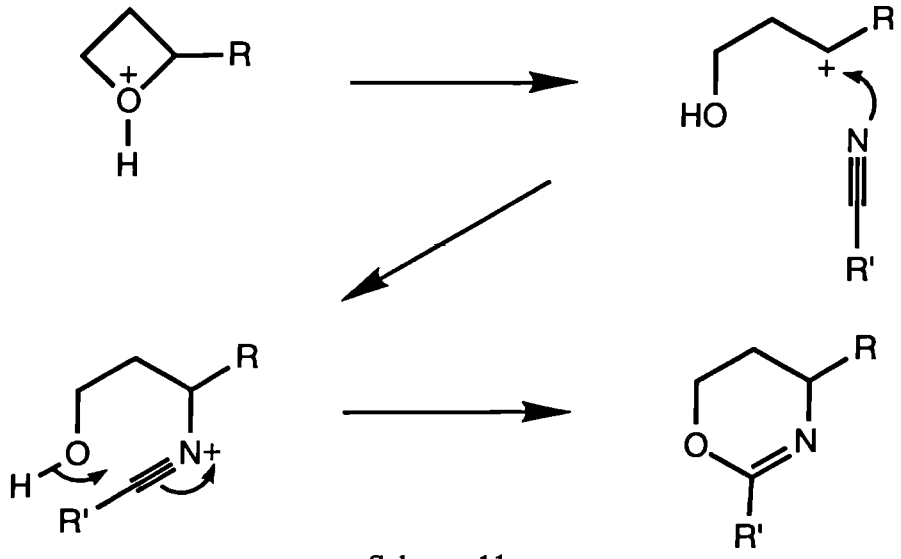
Scheme 9

Oxetanes undergo addition reactions with carbonyl compounds and nitriles in the presence of acid. The reaction of an aldehyde or ketone to give a 2-substituted 1,3-dioxane is a general one and can be used either as a means of protecting a carbonyl group, or of characterising an oxetane (see Scheme 10).



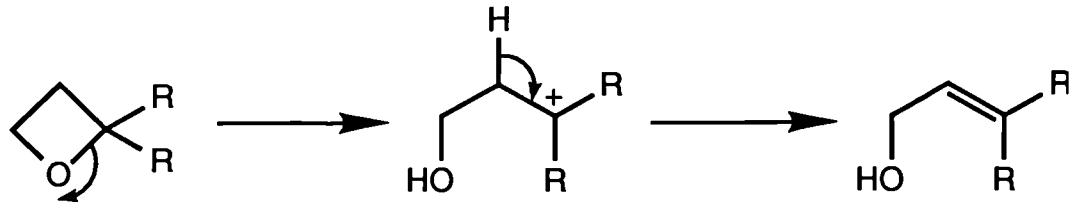
Scheme 10

The corresponding reaction using nitriles in the presence of carbonyl compounds yields 1,3-dihydro-1,3-oxazines (see Scheme 11).



Scheme 11

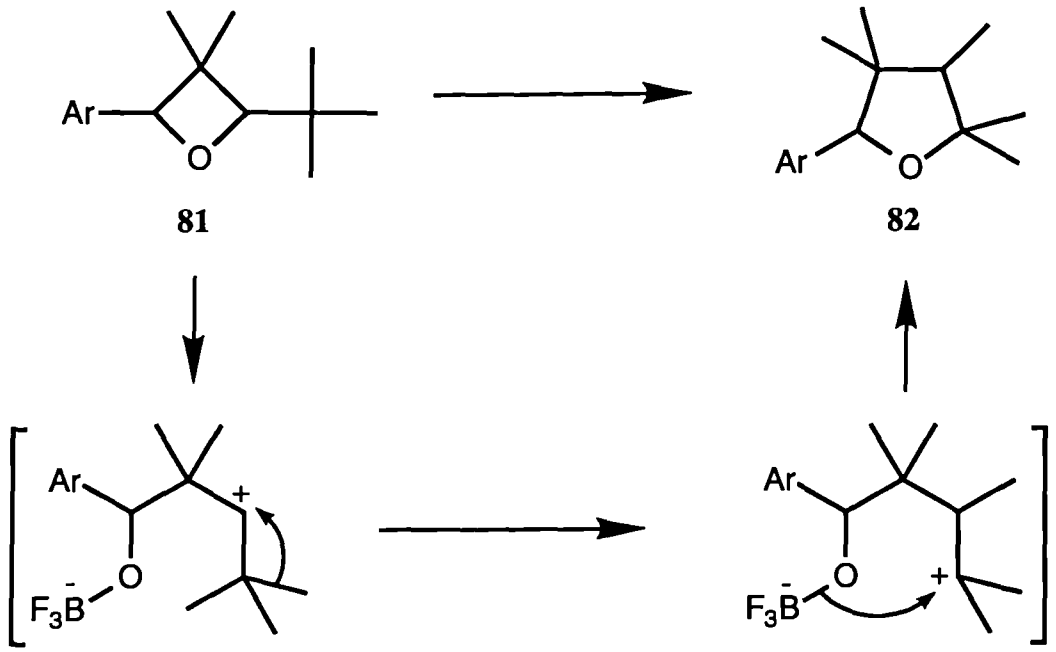
In the absence of a suitable nucleophile, oxetanium ions frequently give products resulting from intramolecular rearrangements. 2,2-Dialkyloxetanes are particularly susceptible to rearrangement on treatment with acid. The reaction proceeds *via* the carbocation, which generally eliminates a proton to give the corresponding allylic alcohol (see Scheme 12).



Scheme 12

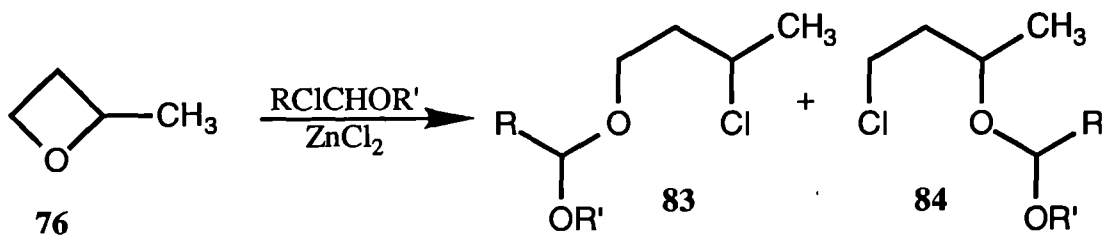
On treatment with Lewis acids, 2-aryl-3,3-dimethyl-4-*t*-butyloxetanes **81** give 2-aryl-3,3,4,5,5-pentamethyltetrahydrofurans **82**.[45] In this case, the formation of a

carbocation at the site of the *t*-butyl substituent formed *via* an S_N1 ring-opening mechanism, induces methyl migration followed by cyclisation to form a five-membered ring (see Scheme 13).



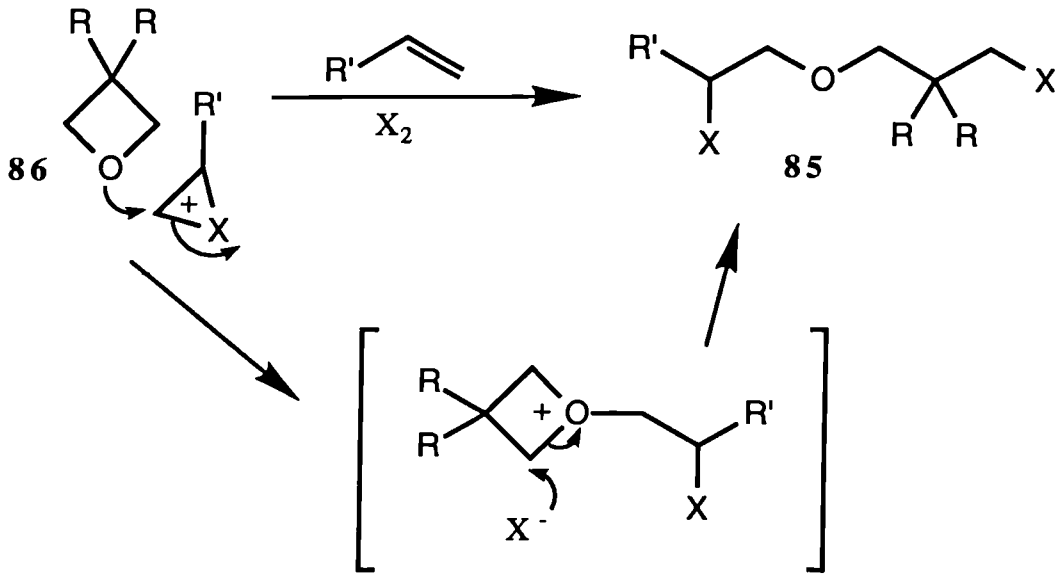
Scheme 13

Alkylation of oxetanes can also cause ring-cleavage. For example, the action of α-chloro ethers in the presence of zinc chloride gives rise to a mixture of products which arise from *O*-alkylation followed by attack of chloride ion. 2-Methyloxetane (**76**) for example, gave a mixture of the acetals **83** + **84**.[46]



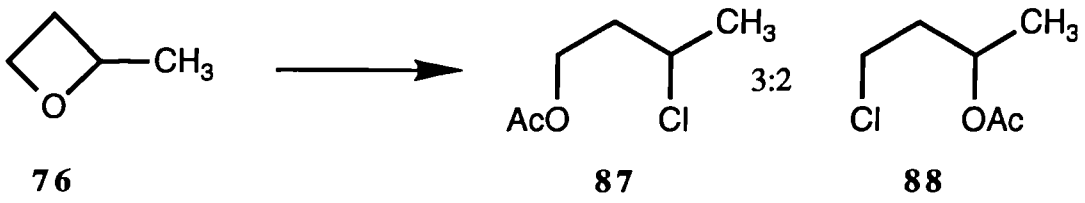
Similar results have been obtained using reactive alkyl halides, such as allyl bromide or benzyl bromide.

Dihalogenated ethers **85** have been prepared from oxetanes by adding the oxetane **86** to an alkene halogenation mixture (see Scheme 14).



Scheme 14

Acyl chlorides react readily with oxetanes to give chloro esters. 2-Methyl-oxetane (**76**) for example, on treatment with acetyl chloride, gave a mixture of 3-chlorobutyl acetate (**87**) and 4-chloro-2-butyl acetate (**88**) in a ratio of 3:2 respectively.[43]



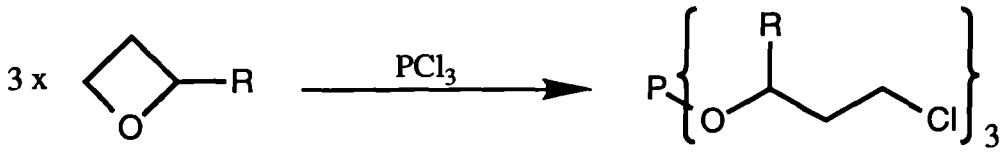
76 **87** **88**

On the other hand, under these conditions 2-phenyloxetane (**89**) yielded only 3-chloro-3-phenylbutyl acetate (**90**).

89 **90**

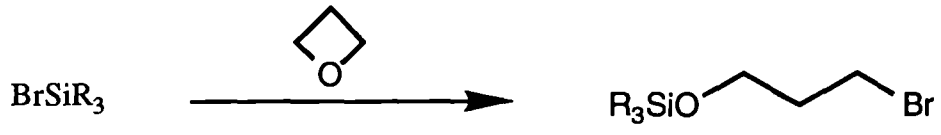
These results suggest that the mechanism is again on the S_N1 / S_N2 borderline. This is probably due to the similarity between an acyloxonium intermediate formed here, and the protonated oxetanium ion formed in aqueous acid (p. 25).

In an analogous reaction, phosphorus halides reacted with oxetanes to give haloalkyl phosphites (see Scheme 15).



Scheme 15

Similarly, trialkylbromosilanes **91** reacted with oxetanes to give trialkylsilyloxy-propyl bromides **92** in good yield.

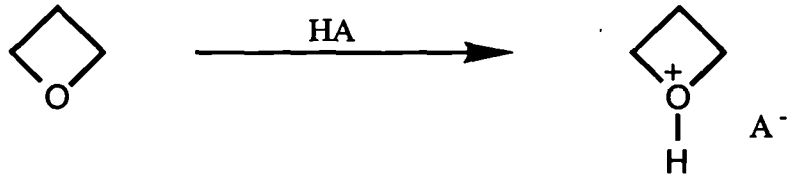


91 **92**

Another important reaction of oxetanes which is initiated by electrophilic attack of the oxetane ring, is polymerisation.

(c) The Cationic Ring-Opening Polymerisation of Oxetanes[47]

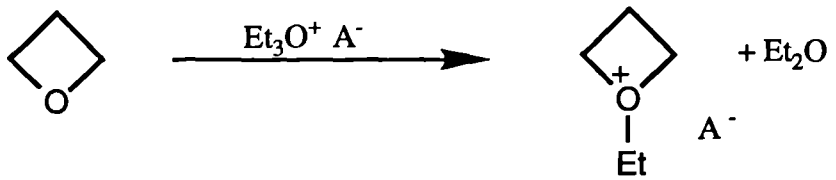
The polymerisation of oxetanes can be initiated by attack of an electrophile on the ring oxygen. The most commonly used electrophile is a proton, and this must be introduced as an acid with a non-nucleophilic conjugate base (A^-), giving the oxetanium ion **93**.



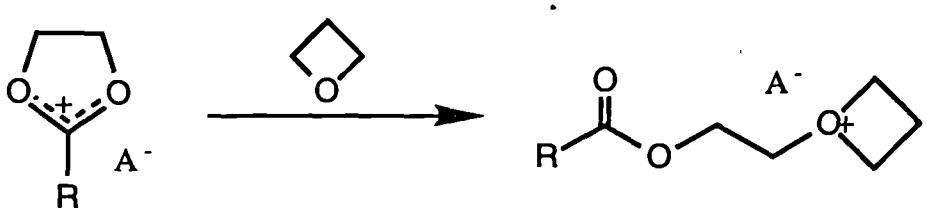
15 **93**

Polymerisation occurring by such a process results in a hydroxyl-terminated polymer.

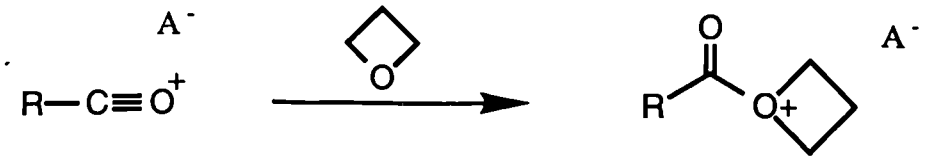
Similarly, a triethyloxonium salt gives a tertiary oxonium salt **94** which results in an ethoxy-terminated polymer. A 1,3-dioxolan-2-ylium salt **95** gives the tertiary oxonium salt **96** which results in an 1-(acyloxy)ethoxy-terminated polymer, and an oxocarbonium salt **97** reacts with the oxetane to yield oxonium salt **98** which results in an acetoxy-terminated polymer. A diphenylmethane salt **99** gives an oxonium salt **100** which results in a diphenylmethoxy-terminated polymer.



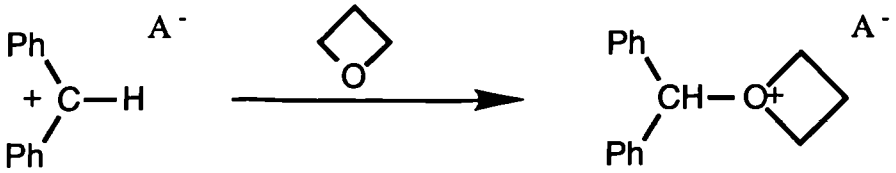
15 **94**



95 **96**

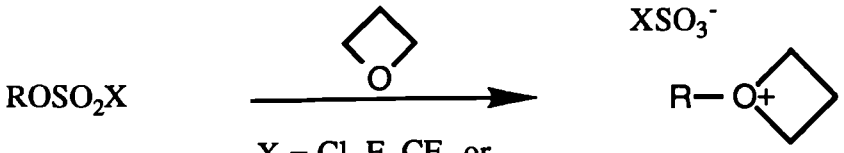


97 98



99 100

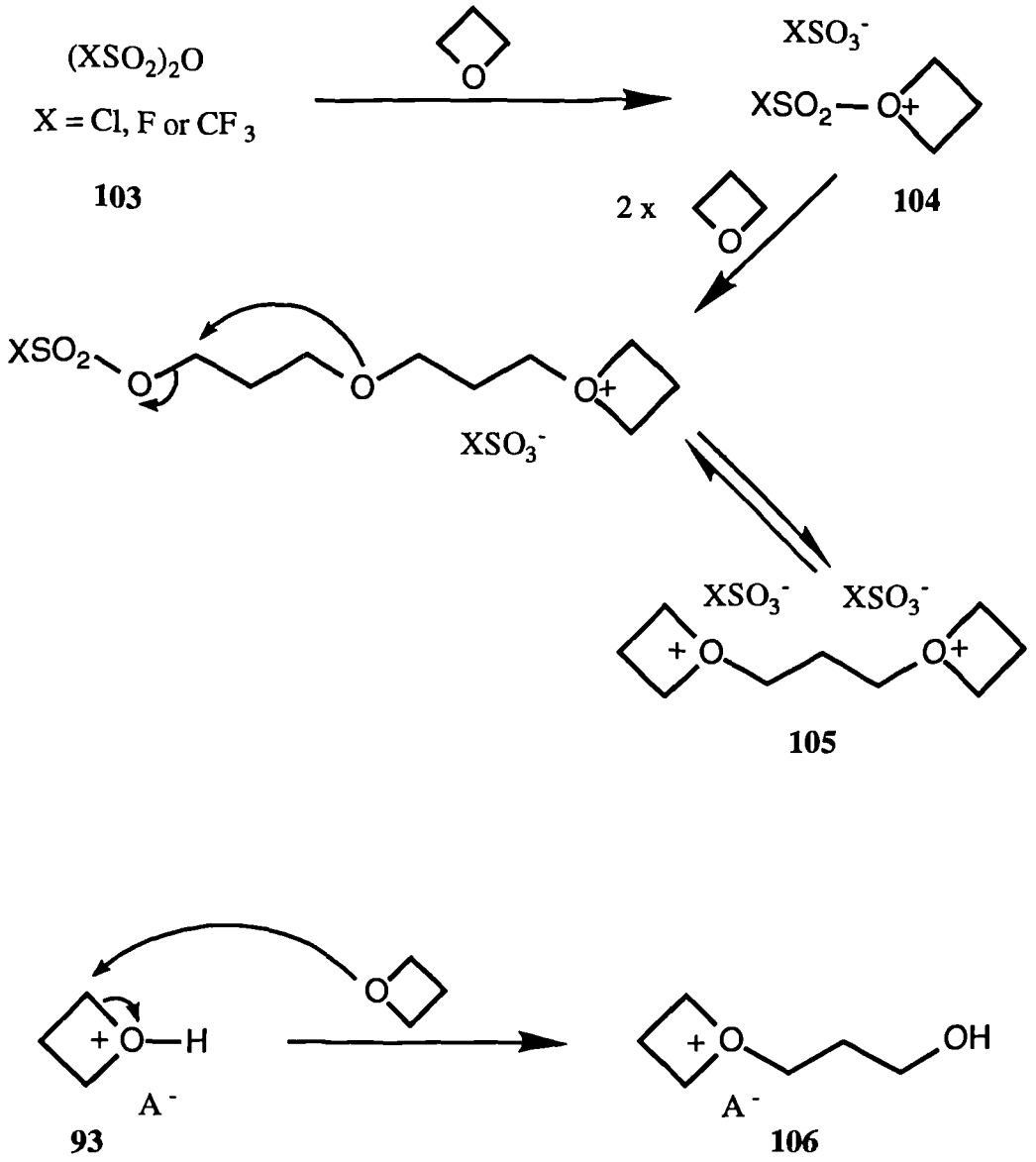
Esters **101** of trifluoromethanesulphonic acid and other 'super-acids', react with oxetanes to give oxonium salts **102** which produce alkyl-terminated polymers.



101 **102**

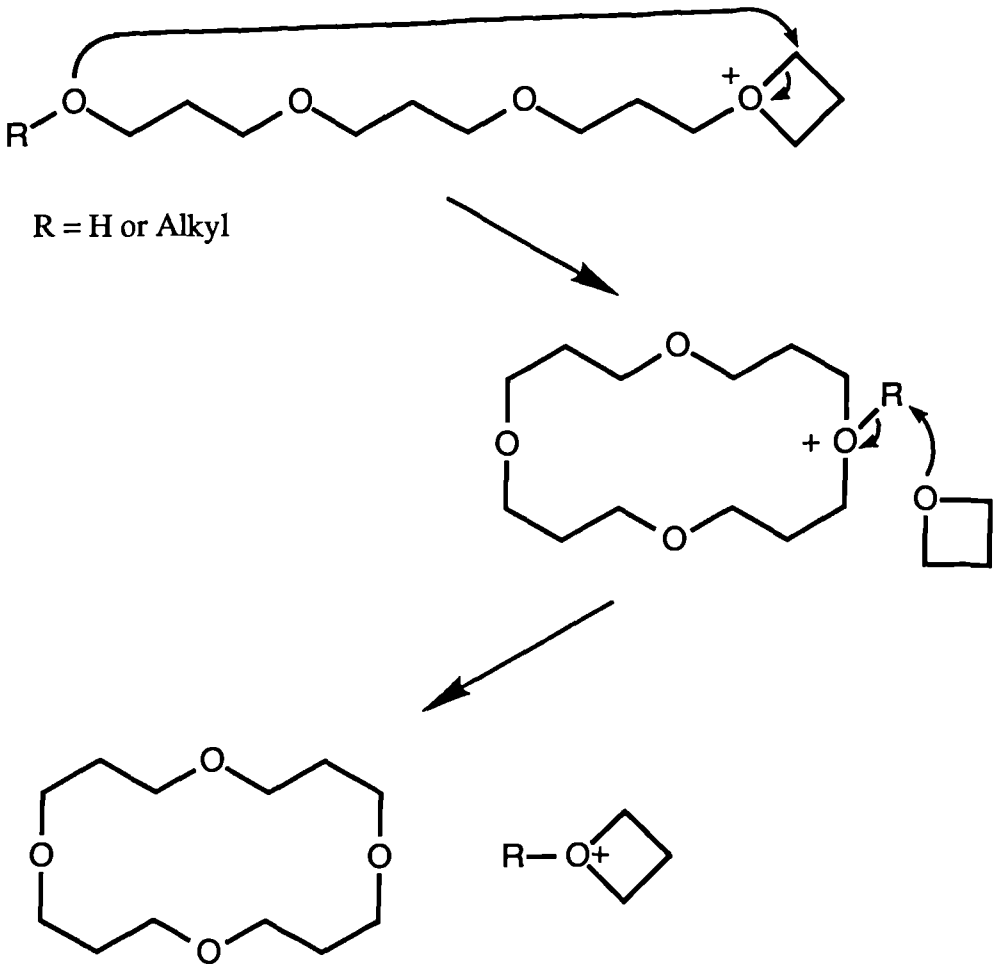
The anhydrides **103** of the 'super-acids' react with oxetanes to give tertiary oxonium ions (*e.g.* **104**) which react with further oxetane molecules to give a di-oxonium ion **105**. Polymerisation is initiated by both of the oxonium moieties, and the anhydrides are therefore bifunctional initiators producing polymers with two highly reactive terminal groups.

In all of the above processes, the chain of the polymer grows due to the attack by an oxetane oxygen at the α-carbon atom of the oxonium species (*e.g.* **93** gives **106**).



Polymerisation then continues until either the supply of monomer is exhausted or until the growing chain is terminated by one of the following processes.

Formation of cyclic oligomers is the major side-reaction associated with the cationic ring-opening polymerisation of oxetanes. In particular, the cyclic tetramer **107** is a common side-product. The oligomers are formed by 'back-biting' reactions involving the attack of an open chain ether oxygen at the α-carbon atom of the oxonium ion. Subsequent salt exchange simply regenerates the original oxetanium ion **108** (see Scheme 16).

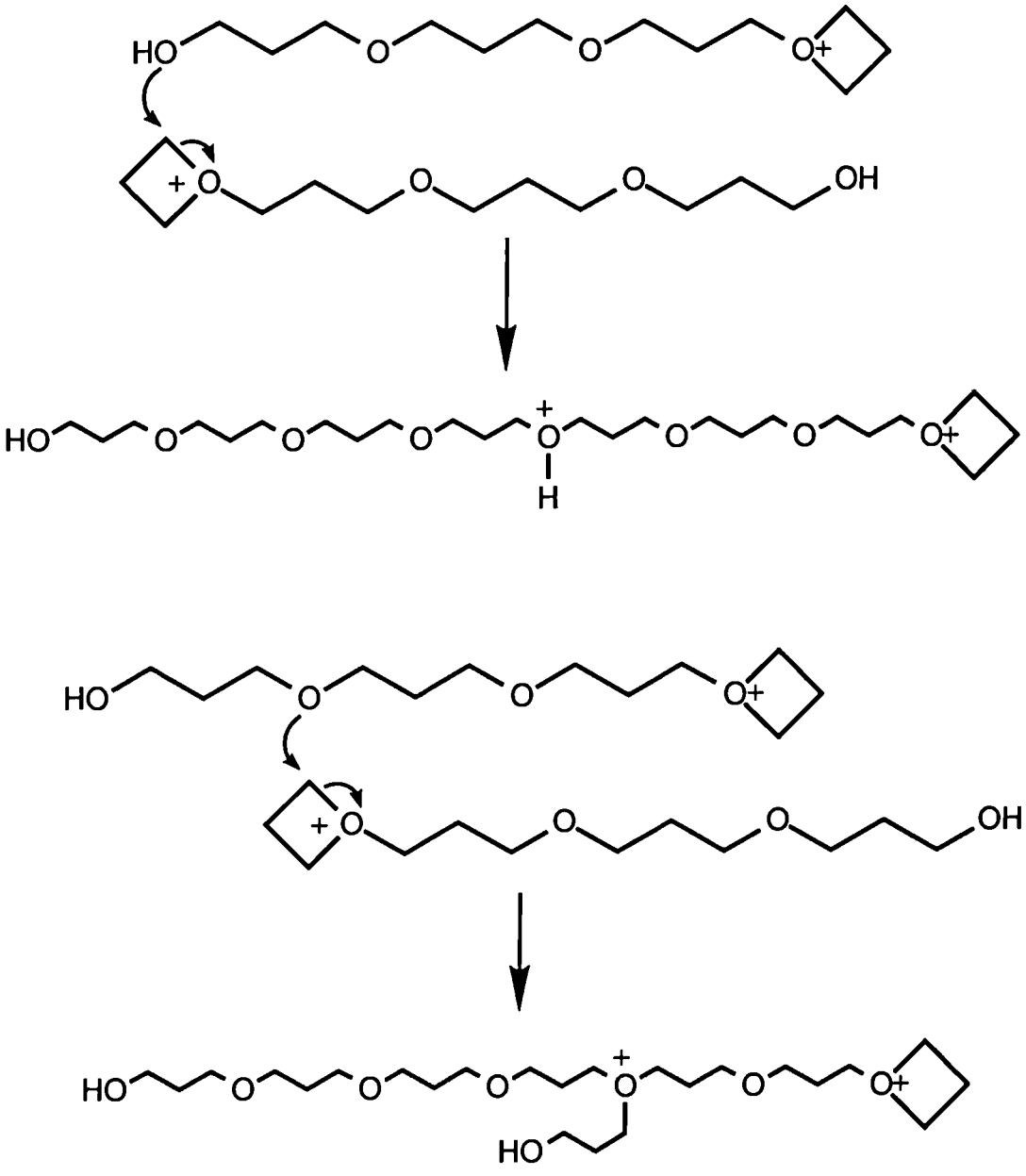


107 **108**

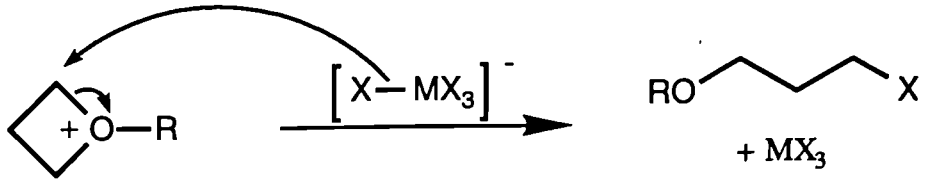
Scheme 16

An intermolecular version of the above reaction results in the formation of either a linear secondary oxonium ion or a tertiary branched oxonium ion depending on which oxygen atom is employed as the nucleophile (see scheme 17).

The attack of an acyclic nucleophile on an oxonium ion is a chain terminating step and attack by the oxonium ion's own counter-ion is no exception. Attack on an oxonium ion by its tetrachloroaluminate or tetrafluoroborate counter-ion is a common termination step, and results in a halogen terminated polymer (see Scheme 18).



Scheme 17

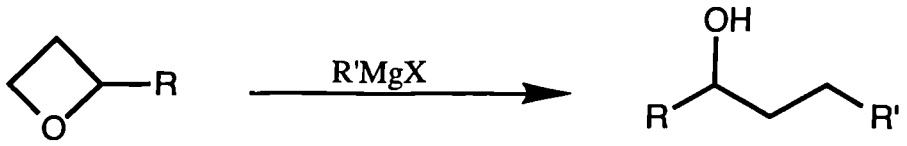


Scheme 18

The side-reactions involved in oxetane polymerisation are generally much reduced compared with other cyclic ether polymerisations. This is due to the greater reactivity of oxetanes, which arises from their exceptional electron donor ability (p. 25).

2. Reactions with Nucleophiles

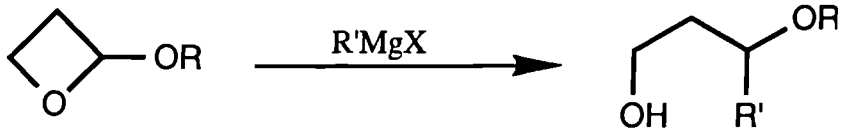
Without acid catalysis, only highly reactive nucleophiles react with oxetanes, and Grignard reagents are probably the single most important group in this category.



Scheme 19

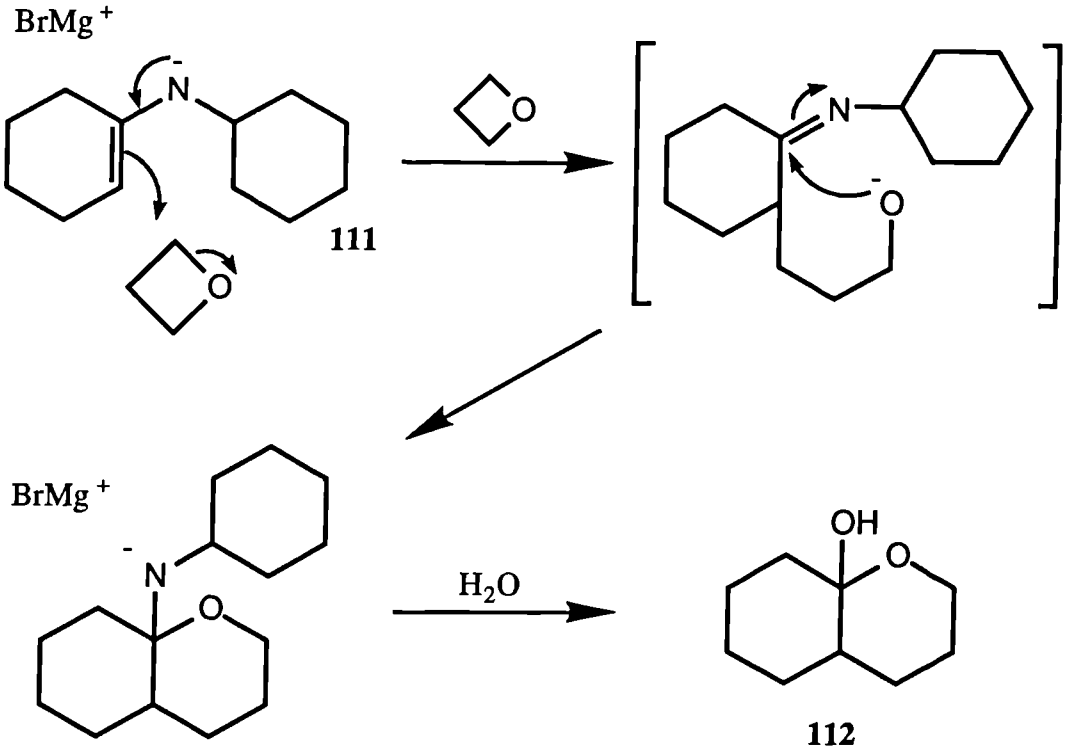
The products are those arising from nucleophilic attack at the least hindered α-carbon atom of the oxetane (see Scheme 19).

2-Alkoxyoxetanes **109** however, react at the 2-position to give good yields of the γ-hydroxy ethers **110**.

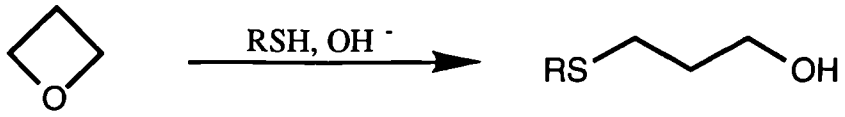


109 **110**

Enol alkylation has been achieved using an oxetane by reacting it with the bromomagnesium *N*-cyclohexylimino derivative **111** of cyclohexane.[48] The product, a bicyclic hemi-acetal **112**, was obtained in 80% yield.

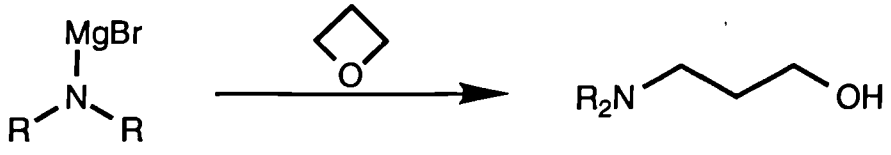


Oxetanes react readily with thiols in the presence of alkali to give γ-hydroxy thioethers (see Scheme 20).



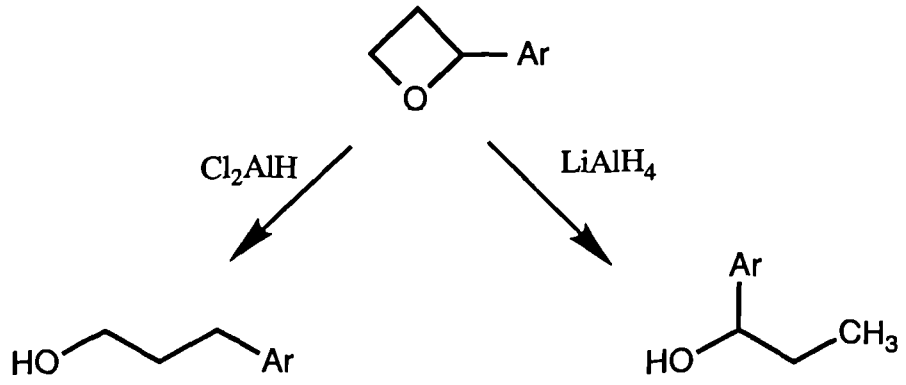
Scheme 20

The corresponding reaction of primary and secondary amines is much slower and requires higher temperatures. An alternative reaction is that of the bromomagnesium amides **113** with oxetanes which gives good yields of 3-hydroxypropylamines **114**.



113 **114**

Reduction of oxetanes with lithium aluminium hydride causes ring fission between oxygen and the least substituted of the α-carbon atoms. 2-Aryloxetanes are cleaved to give the alternative isomer when dichloroaluminium hydride is employed as the reducing agent (see Scheme 21).



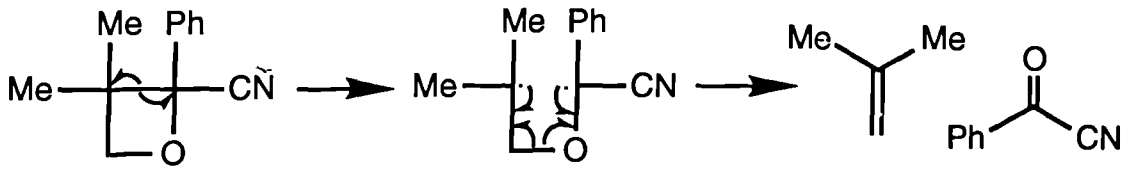
Scheme 21

Clearly, the mechanism is determined by the nucleophilicity of the reducing agent. The more nucleophilic reagent, lithium aluminium hydride, promotes an S_N2 reaction, whereas the weaker nucleophile, dichloroaluminium hydride promotes an S_N1 reaction.

3. Photolysis and Thermolysis

The thermal decomposition of oxetanes occurs around 300-450°C and gives the products of a reverse [2+2] cycloaddition, namely an alkene and a carbonyl compound. The reaction is a two-stage process. Initially, homolytic fission gives a 1,4-biradical, the reaction showing little selectivity in simple alkyl substituted oxetanes. However, when aromatic or unsaturated groups are present, some regioselectivity is found. For example, 2-cyano-3,3-dimethyl-2-phenyloxetane (**115**) on thermolysis gave *iso*-butene (**116**) and benzoyl cyanide (**117**),[50] the products presumably arising from decompos-ition of the

stabilised biradical **118**.



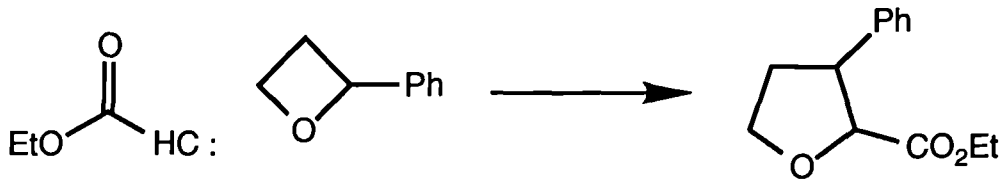
115 **118** **116** **117**

The photolyses of oxetanes give products similar to those arising from thermolysis. In general, less selectivity is apparent in photolyses.

4. Other Reactions of Oxetanes

Oxetanes have been found to undergo photochlorination with *t*-butyl hypochlorite to give 2-chloro-oxetanes. These products are extremely unstable and decompose in air.

Carbene insertion into an oxetane ring has been achieved using ethoxycarbonylcarbene (**119**).[51] Thus, 2-phenyloxetane (**120**) gave the ring-expanded 2-ethoxycarbonyl-3-phenyltetrahydrofuran (**121**).



119 **120** **121**

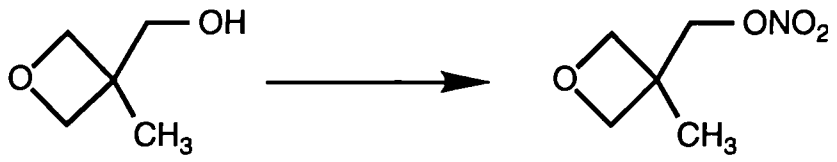
On the other hand, a similar reaction using carbonylcarbene gave only the fragmentation products: carbon monoxide, cyclopropane, propene, ethylene and ketene.[52]

RESULTS AND DISCUSSION

INTRODUCTION

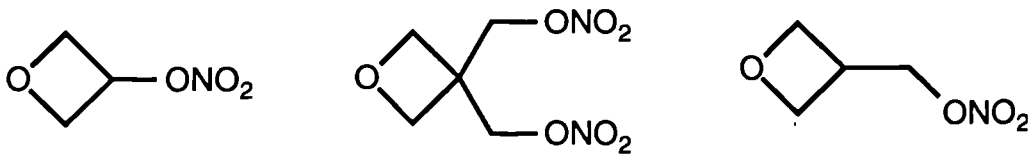
Polymers derived from oxetanes have found use in energetic binder systems for explosives and propellants (see p. 8). Suitable oxetanes are those bearing energetic substituents such as nitrate esters or azides. Previous work has shown that the oxetanes most likely to produce polymers with the desired mechanical properties, are those with no substituents in the 2- or 4-positions.

At present, a polymer of 3-methyl-3-(nitratomethyl)oxetane (**11**) is used in such systems. The oxetane is prepared from 3-(hydroxymethyl)-3-methyloxetane (**122**), a commercially available compound, by nitration using dinitrogen pentaoxide.



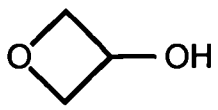
122 **11**

However, three other oxetanes have been identified as potentially useful monomers: 3-nitrato-oxetane (**123**), 3,3-bis(nitratomethyl)oxetane (**124**) and 3-(nitratomethyl)-oxetane (**125**). Each of these simple 3-substituted oxetanes has an oxygen balance superior to that of the currently used molecule, and each should be available by nitration of its corresponding alcohol.

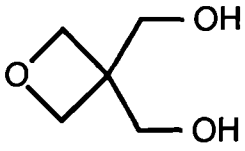


123 **124** **125**

The aim of this project was to investigate and, if possible, improve the routes to two of these hydroxylic precursors: 3-hydroxyoxetane (**127**) and 3,3-bis(hydroxymethyl)oxetane (**24**), and to devise a synthesis of the third, and previously unknown alcohol: 3-(hydroxymethyl)oxetane (**126**).



127



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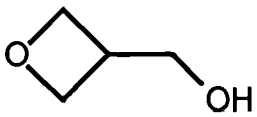
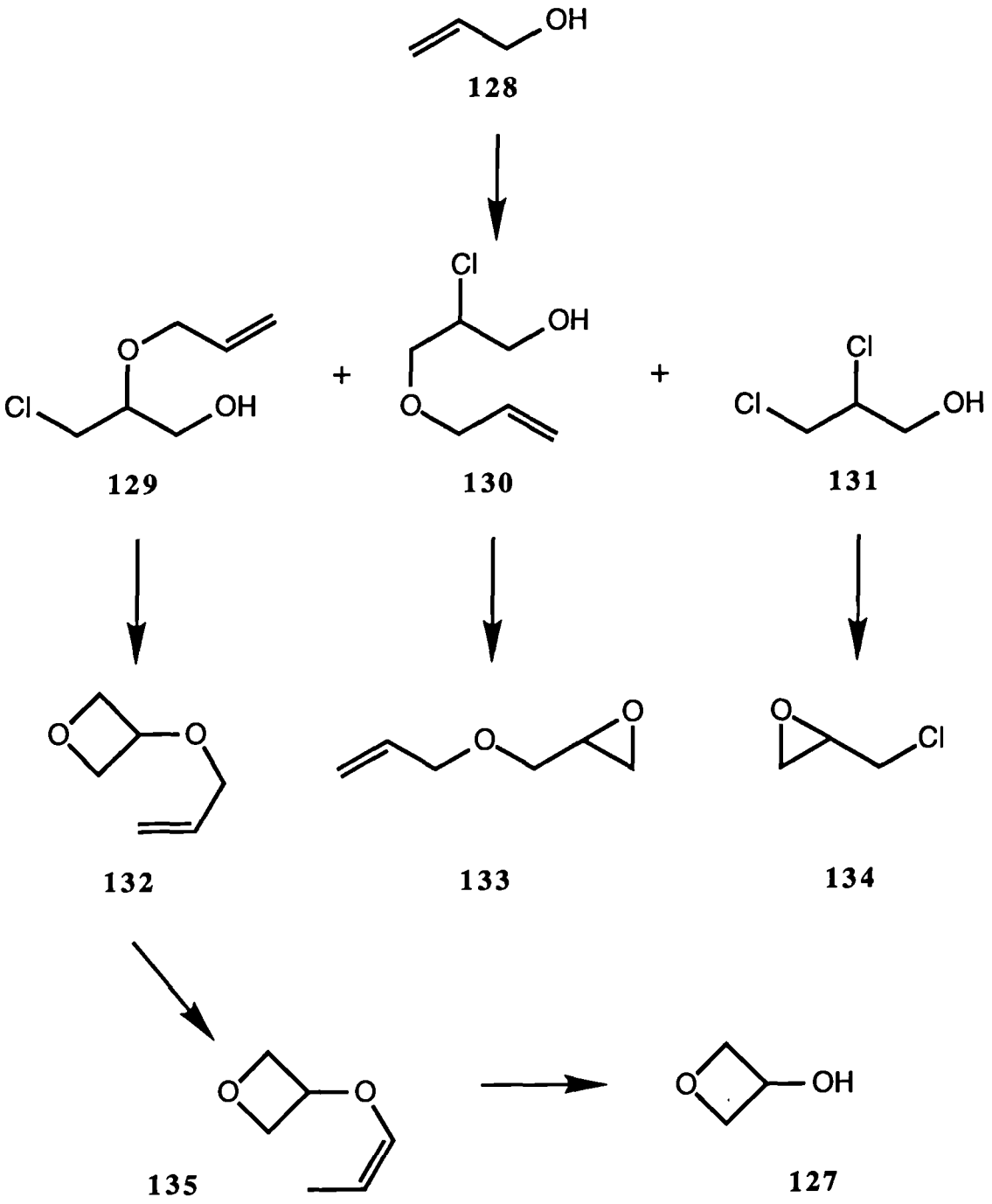


126

THE SYNTHESIS OF 3-HYDROXYOXETANE

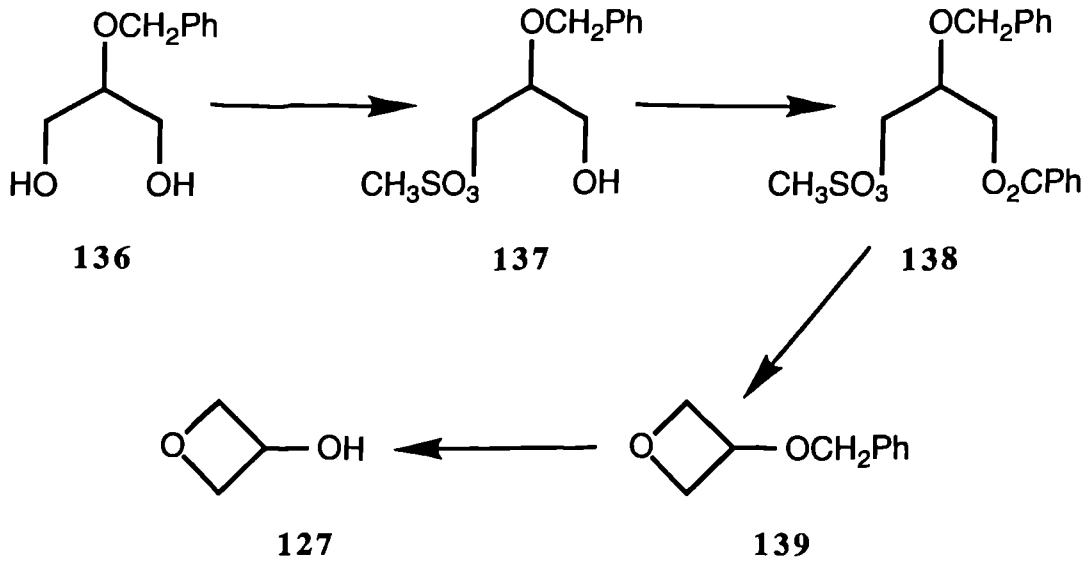
3-Hydroxyoxetane has been synthesised previously in three ways. Wojtowicz and Polak[53] employed a four step route (Scheme 22) from allyl alcohol (**128**).



Scheme 22

The reaction of the alcohol **128** with chlorine gas produced a mixture of 2-allyloxy-3-chloropropan-1-ol (**129**), 3-allyloxy-2-chloropropan-1-ol (**130**) and 2,3-dichloropropan-1-ol (**131**). This mixture was then treated with hot aqueous sodium hydroxide to give a mixture of 3-allyloxyoxetane (**132**), allyl glycidyl ether (**133**) and epichlorohydrin (**134**). The oxetane was separated from the mixture by distillation, isomerised with potassium *t*-butoxide in dimethylsulphoxide, and the resulting *cis*-3-(1-propenoxy)oxetane (**135**) underwent acid-catalysed hydrolysis to give 3-hydroxyoxetane (**127**). With an overall yield of only 2%, this route is clearly not a practical one.

Wang *et al.*[54] also employed a four step route (Scheme 23) for the synthesis of 3-hydroxyoxetane.

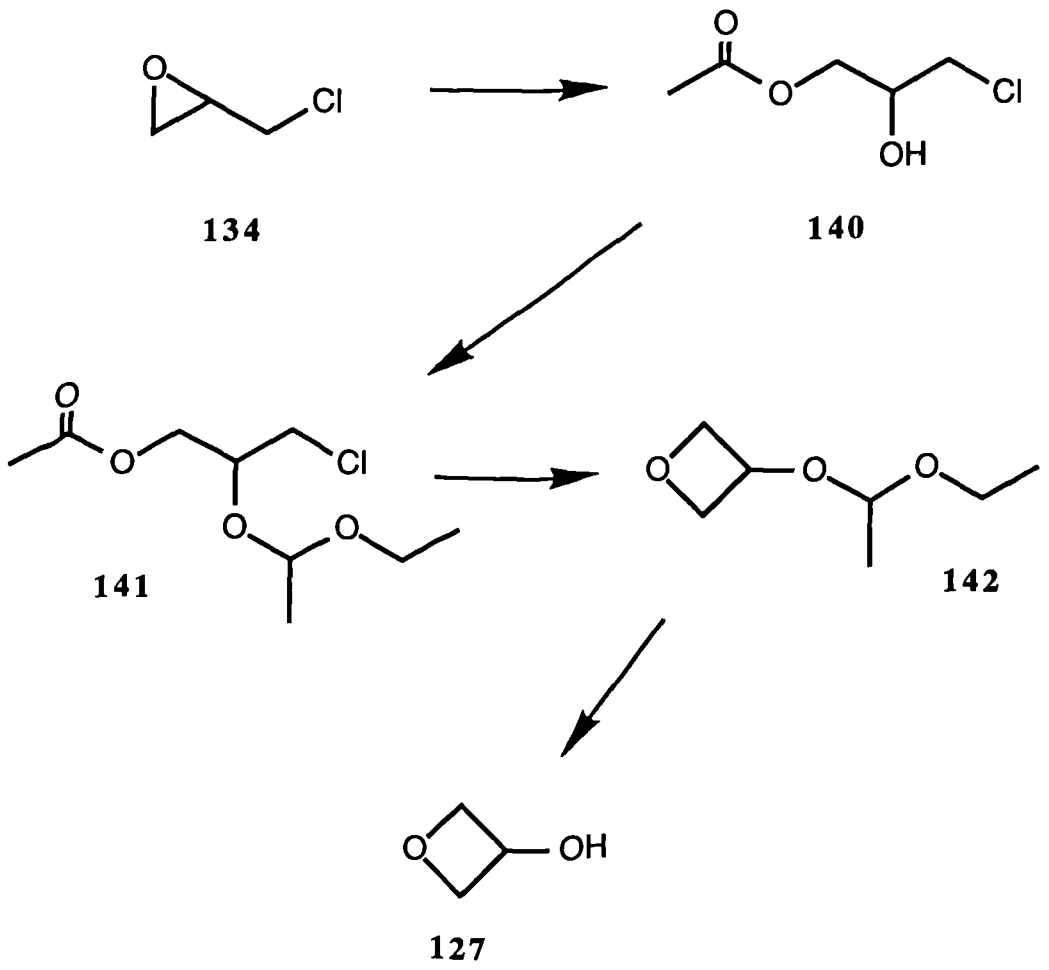


Scheme 23

2-Benzyloxypropane-1,3-diol (**136**) was treated with methanesulphonyl chloride in base to give the mono-methanesulphonate ester **137** which, with benzoyl chloride, yielded the benzoate ester **138**. Cyclisation of this compound using sodium methoxide in methanol gave a 30% yield of 3-benzyloxyoxetane (**139**) from which 3-hydroxyoxetane (**127**) was obtained by hydrogenolysis over a palladium catalyst. No

yield was quoted for this last stage.

Yet another four step synthesis of 3-hydroxyoxetane was that reported by Baum *et al.* (Scheme 24).[55]



Scheme 24

Starting from epichlorohydrin (**134**), ring-opening catalysed by iron (III) chloride in acetic acid gave 3-chloro-2-hydroxypropyl acetate (**140**). Protection of alcohol **140** using ethyl vinyl ether with *p*-toluenesulphonic acid as catalyst, yielded 3-chloro-2-(1-ethoxyethoxy)propyl acetate (**141**), which on cyclisation with hot aqueous potassium hydroxide, gave 3-(1-ethoxyethoxy)oxetane (**142**). This was deprotected, using *p*-toluenesulphonic acid in methanol, to 3-hydroxyoxetane (**127**) in

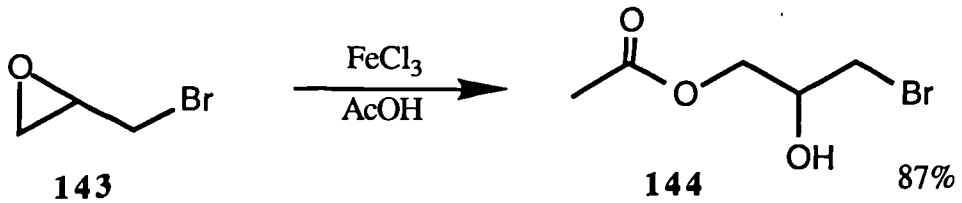
30% overall yield. No intermediates were isolated and characterised during this synthesis.

The third of the above routes seems clearly the most efficient since it offers the highest overall yield and uses only readily available reagents. However, several attempts to prepare a sample of 3-hydroxyoxetane *via* this route failed. The synthesis was therefore examined in detail.

Epichlorohydrin (**134**) was ring-opened using a single equivalent of acetic acid containing a catalytic amount of iron (III) chloride. After distillation, a 57% yield of 3-chloro-2-hydroxypropyl acetate (**140**) was obtained. Protection of alcohol **140** using ethyl vinyl ether with *p*-toluenesulphonic acid as the catalyst gave 3-chloro-2-(1-ethoxyethoxy)propyl acetate (**141**) in 40% yield after isolation by column chromatography. Cyclisation of chloro-ester **141** was carried out in hot, concentrated potassium hydroxide and a 36% yield of 3-(1-ethoxyethoxy)oxetane (**142**) was obtained after distillation.

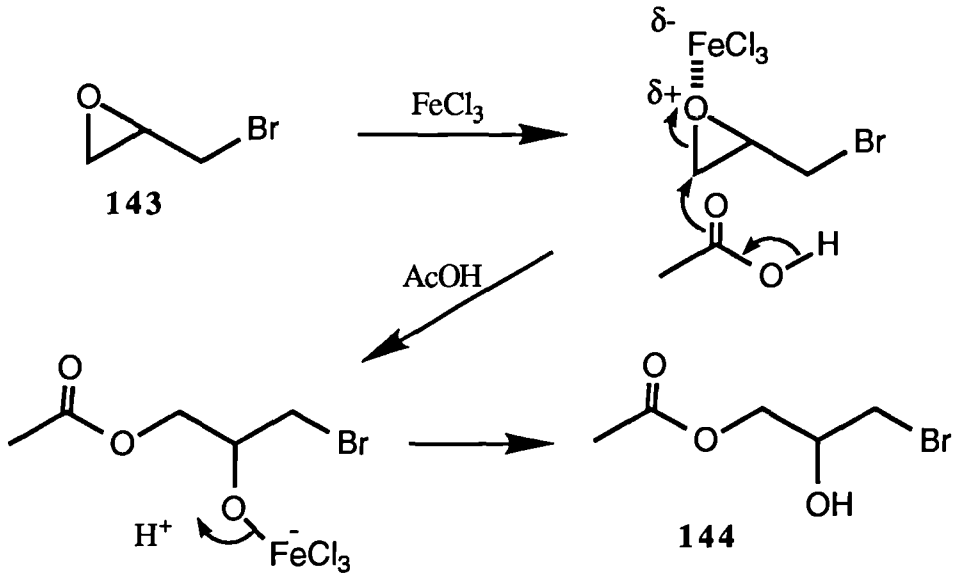
Attempted deprotection of the oxetane using *p*-toluenesulphonic acid in methanol gave only a complicated mixture of products. It seems likely that the failure of this fourth and final step, is the reason for the failure of the overall route in our hands.

The first improvement to the synthesis came with the use of epibromohydrin (**143**) rather than epichlorohydrin (**134**). Addition of epoxide **143** to a solution of iron (III) chloride in acetic acid resulted in a highly exothermic reaction which was complete after 24 hours at room temperature, and 3-bromo-2-hydroxypropyl acetate (**144**) was isolated in 87% yield after removal of the iron (III) chloride by extraction into water.



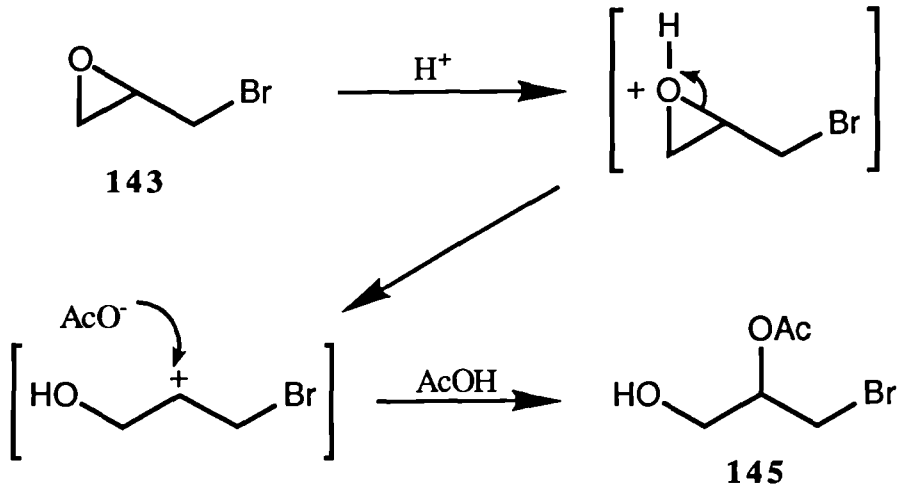
143 **144** 87%

The role of the iron (III) chloride in this reaction is important. The Lewis-acid chelates to the epoxide oxygen and, by withdrawing electron density from the ring, promotes nucleophilic attack at the epoxide. Attack takes place exclusively at the least hindered centre, as would be expected for an S_N2 mechanism, giving 3-bromo-2-hydroxypropyl acetate (**144**) (see Scheme 25).



Scheme 25

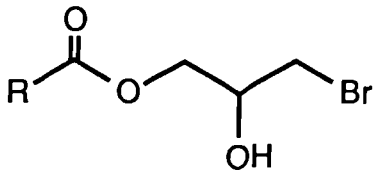
The use of an acid catalyst in this reaction would be expected to give a different product (see Scheme 26). Protonation of the epoxide **143** should result in ring-opening



Scheme 26

to give a secondary carbocation, which would then undergo nucleophilic attack to give 2-acetoxy-3-bromopropan-1-ol (**145**) as the major product. None of this primary alcohol **145** was observed in our reaction product.

The nature of the nucleophile should also affect the rate and yield of the reaction. Four other acids were used in the ring opening step. Propionic acid, chloroacetic acid, dichloroacetic acid and trifluoroacetic acid, all underwent exothermic reactions with epibromohydrin. In each case, the product **146** was isolated in moderate to good yield, except for the trifluoroacetate ester (**146**, R = CF_3) which could not be purified by distillation, chromatography or by partitioning between diethyl ether and water.



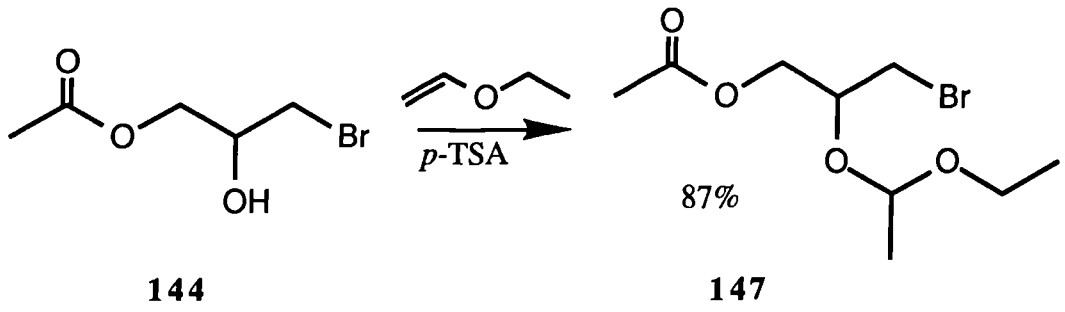
146

Acid (RCO_2H)	Yield (%) of ester **146**
R = CH_3	87
R = CH_3CH_2	61
R = $ClCH_2$	82
R = Cl_2CH	64
R = F_3C	--

Table 1

Protection of the 3-bromo-2-hydroxypropyl acetate (**144**) with ethyl vinyl ether and *p*-toluenesulphonic acid catalysis, consistently gave a black tar despite strict temperature control. The protected alcohol **147** was isolated in only 40% yield from the crude product.

An attempt was made to improve the reaction by reducing the rate of reaction. Diluting the previously solventless reaction with diethyl ether offered no improvement in yield, and no significant reduction in tar formation. Another attempt to improve the reaction, using cobalt (II) chloride in acetonitrile[56] as catalyst instead of *p*-toluene-sulphonic acid, produced a complex mixture of products which was not investigated further. Finally an 87% yield of 3-bromo-2-(1-ethoxyethoxy)propyl acetate (**147**) was obtained by using ethyl vinyl ether which had been freshly distilled from sodium metal before use, with *p*-toluenesulphonic acid as the catalyst.



144 **147**

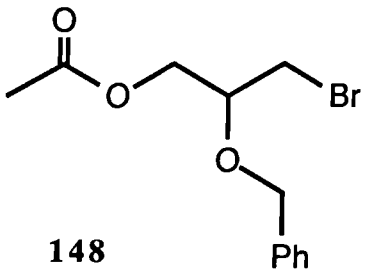
Protection of the monochloro- and dichloro-acetate esters with ethyl vinyl ether gave products which could not be characterised satisfactorily. Since the reaction proceeded well with acetate ester **144**, no further reactions were attempted with these other esters.

The use of a *t*-butyldimethylsilyl ether as a protective group was next investigated. As a protective group this silyl ether is generally superior to an acetal, such as that derived from ethyl vinyl ether, both in stability and in ease of deprotection under mild conditions.

Treating 3-bromo-2-hydroxypropyl acetate (**144**) with *t*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide,[57] the conditions used routinely for such protective reactions, yielded none of the expected, protected product. A second, and much more forcing set of conditions was employed. Treatment of the alcohol **144**

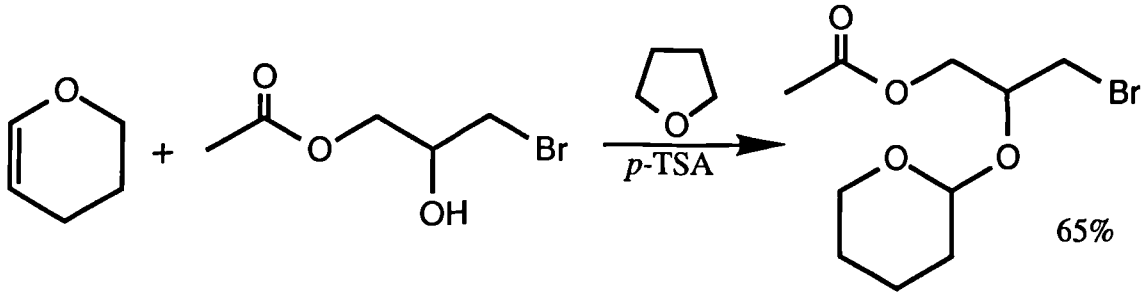
with *t*-butyldimethylsilyl chloride and lithium sulphide in acetonitrile, conditions normally used to protect secondary or particularly hindered alcohols,[58] also failed to give any silyl ether. The failure of this reaction is probably due to steric hindrance of the incoming protective group by the large acetoxymethyl group.

An attempt to prepare 2-benzyloxy-3-bromopropyl acetate (**148**), using benzyltrichloroacetimidate in dichloromethane and cyclohexane with trifluoromethane-sulphonic acid as the catalyst,[59] produced none of the expected product. Again, this may be due to steric inhibition of the incoming protective group.



148

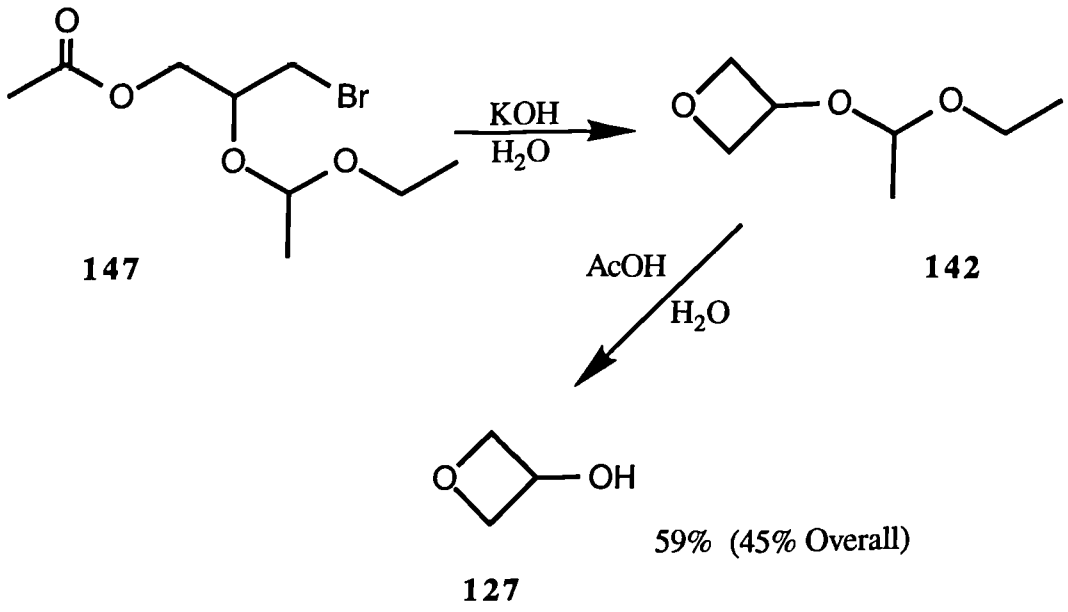
The reaction of 2,3-dihydropyran (**149**) with 3-bromo-2-hydroxypropyl acetate (**144**), under conditions similar to those used for the ethyl vinyl ether protection, produced a 65% yield of acetal **150**.



149 **144** **150**

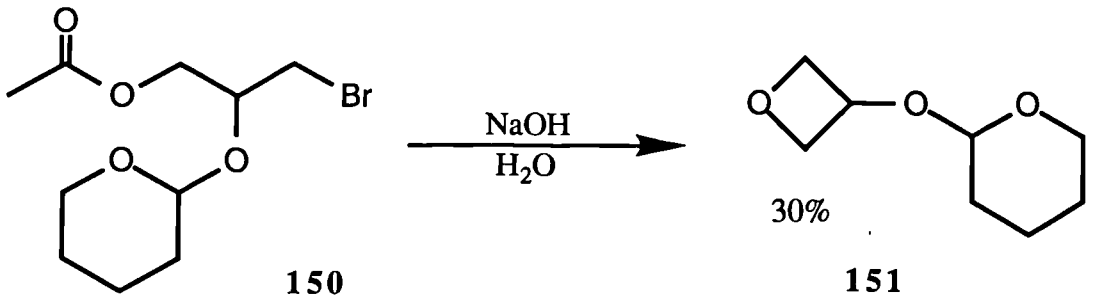
3-Bromo-2-(1-ethoxyethoxy)propyl acetate (**147**) was cyclised according to the method of Baum *et al.*[55] and the crude 3-(1-ethoxyethoxy)oxetane (**142**) obtained was deprotected using dilute aqueous acetic acid. Hydrolysis of acetal **142** in dilute acetic acid was found to be superior to hydrolysis in methanolic *p*-toluenesulphonic acid as

the latter gave a more complex mixture of products (p. 49). By keeping the amount of water used to a minimum, it was possible to isolate crude 3-hydroxyoxetane (**127**) by dissolving the entire reaction mixture in ethyl acetate, neutralising the acid with solid sodium hydrogen carbonate, and removing any remaining water by desiccation of the solution using magnesium sulphate.



147 **142** **127**

The yield for these last two steps was 59% giving an overall yield of 45% from epibromohydrin. This clearly compares favourably with the overall yield of 30% reported for the literature synthesis,[55] which, in our hands, could not be repeated.

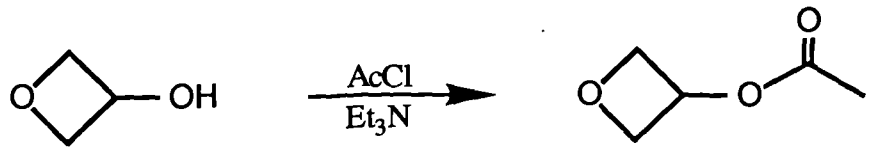


150 **151**

Cyclisation of the tetrahydropyranyl ether **150** under conditions similar to those used above, afforded 3-(2-tetrahydropyranyloxy)oxetane (**151**) in only 30% yield, and

as this yield was much lower than that of the 1-ethoxyethoxy-compound **142**, no further use was made of this compound.

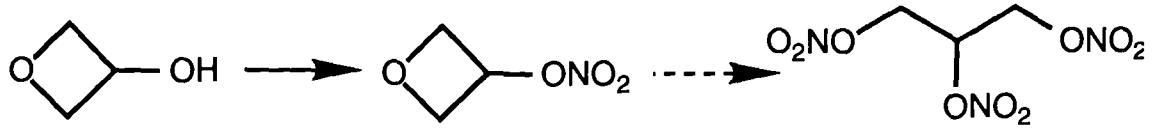
A sample of 3-hydroxyoxetane (**127**) was esterified, using acetyl chloride and triethylamine, to give 3-acetoxyoxetane (**152**) in 76% yield. This material was then used to confirm that 3-acetoxyoxetane is a minor contaminant in the 3-hydroxyoxetane obtained *via* the above route, and also to further characterise 3-hydroxyoxetane, since its proton magnetic resonance spectrum (p. 105) is simpler than that of the parent alcohol.



76%

127 **152**

3-Hydroxyoxetane (**127**) was nitrated using a solution of dinitrogen pentaoxide[60] in dichloromethane and at low temperature to give 3-nitrato-oxetane (**123**). This result is significant, as any nitration under the acidic conditions normally associated with such a reaction, would be expected to give nitroglycerine (**2**) and would therefore necessitate the separation of two toxic and explosive compounds.

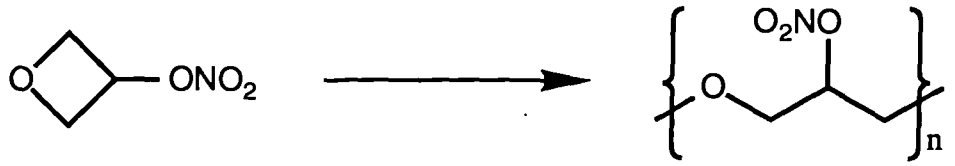


127 **123** **2**

When analysed by high performance liquid chromatography, the 3-nitrato-oxetane obtained from this reaction was shown to contain no nitroglycerine.

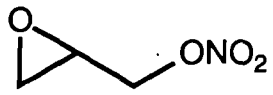
A sample of 3-nitrato-oxetane (**123**) was polymerised in dichloromethane using tetrafluoroboric acid as the catalyst, to give poly-3-nitrato-oxetane (**153**) with an

average molecular mass of 1640 (n≈14).

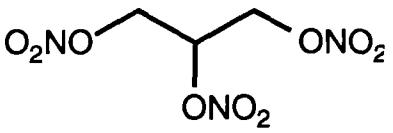


123 **153**

The polymer, a viscous oil, had a glass transition temperature (Tg) of -22.7°C which is too high for the polymer to be of much use as an energetic binder (see p. 8). However, co-polymers of 3-nitrato-oxetane with other energetic monomers such as glycidyl nitrate (**13**) or polymers plasticised with other energetic molecules such as nitroglycerine (**2**), could have much lower Tg values.



13



2

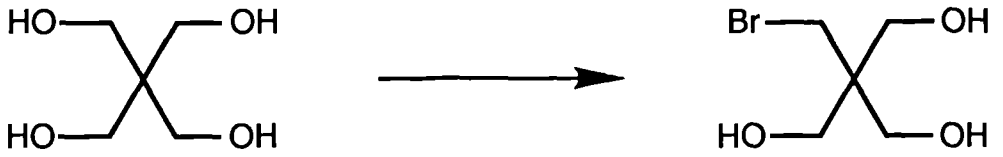
3-Nitrato-oxetane is still therefore of potential use in energetic binder systems for use in explosives or propellants.

THE SYNTHESIS OF 3,3-BIS(HYDROXYMETHYL)OXETANE

3,3-Bis(hydroxymethyl)oxetane has been synthesised previously in three ways. Govaert and Beyaert[13] produced the oxetane (**24**) by treating 2-(bromomethyl)-2-(hydroxymethyl)propane-1,3-diol (**154**) with strong base. Although this Williamson

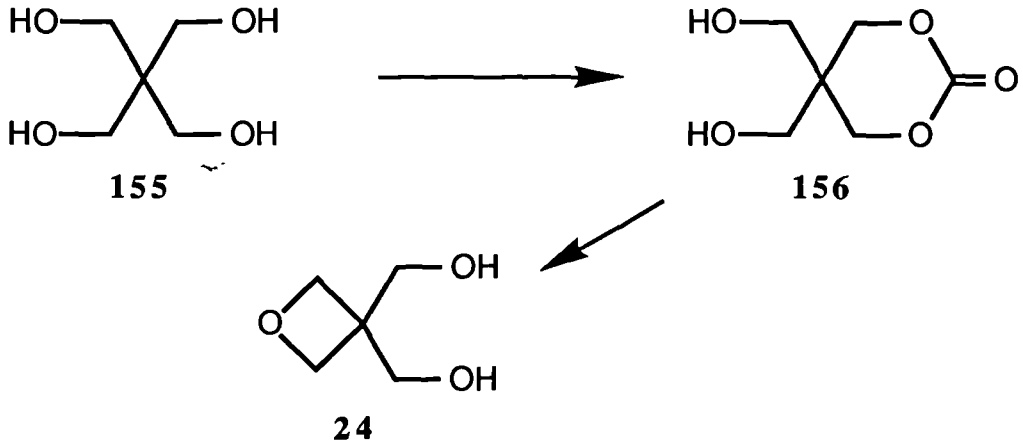
154 **24**

reaction produced a good (75%) yield for an oxetane ring-closure reaction, it suffers from having a relatively inaccessible starting material. The preparation of bromohydrin **154** has been studied extensively,[61-66] and yields of up to 65% were reported[61] for the nucleophilic substitution of pentaerythritol (**155**). However, the bromination is difficult, and the mixture of mono- and di-bromides formed must be separated by fractional crystallisation.



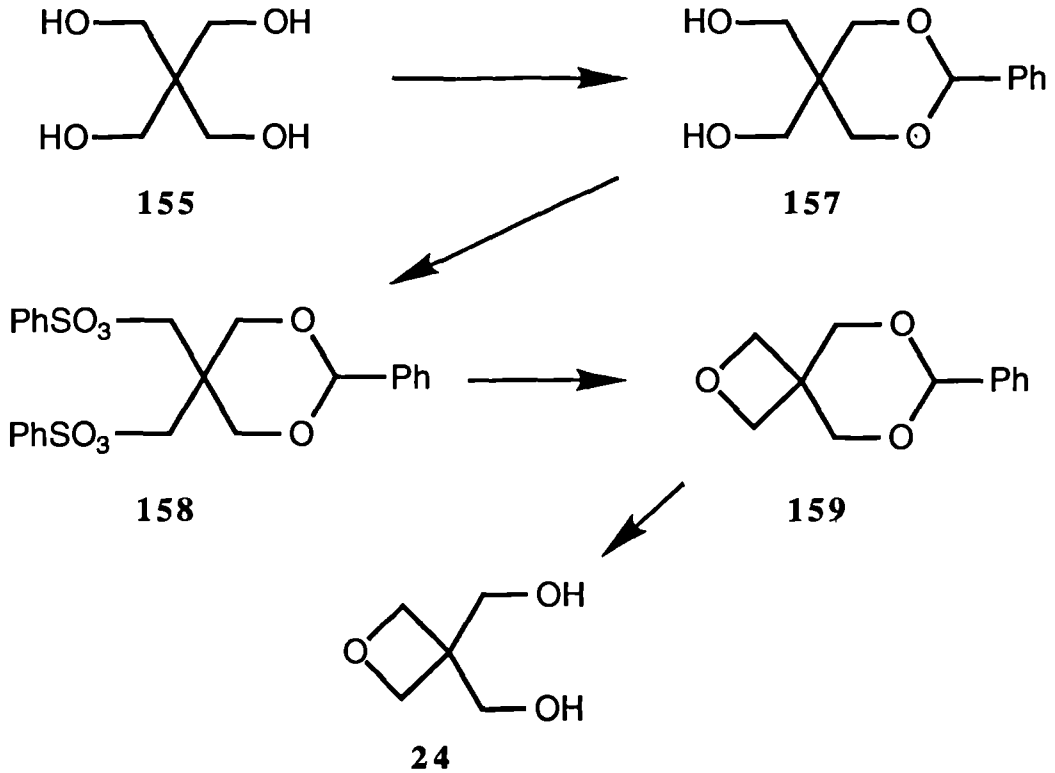
155 **154**

Pattison[22] reported a one-pot, two stage process involving the pyrolysis of an intermediate carbonate ester. Pentaerythritol (**155**) was added to a refluxing solution of potassium hydroxide in diethyl carbonate. The resulting carbonate ester **156** was pyrolysed at 170°C and 3,3-bis(hydroxymethyl)oxetane (**24**), which distilled from the mixture, was obtained in an overall yield of 34%.



The presence of the hydroxymethyl substituents in carbonate ester **152**, results in its unusually low decomposition temperature (see p. 18).

The third synthesis of 3,3-bis(hydroxymethyl)oxetane, that by Jakobiek,[67] also begins with pentaerythritol (**155**). The alcohol **155** was converted into monobenzal acetal **157** using benzaldehyde and acid. Further treatment of the monobenzal with benzenesulphonyl chloride and base, afforded bis(benzenesulphonate) **158**. Cyclisation of the sulphonate ester, using concentrated potassium hydroxide, yielded the expected

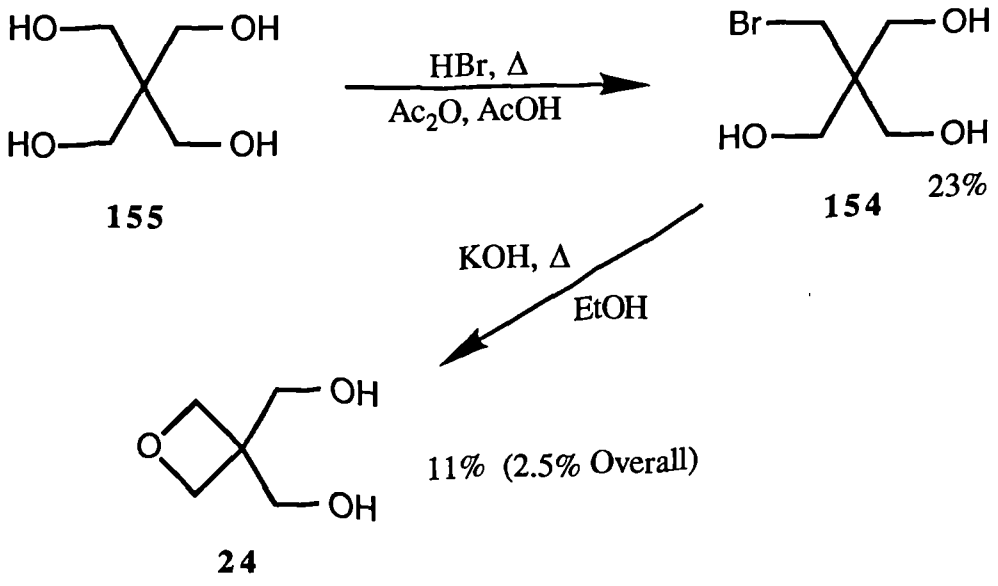


spiro-oxetane, 7-phenyl-2,6,8-trioxa spiro[3.5]nonane (**159**). Finally, the benzal group was removed in aqueous acetic acid to give the oxetane **24**.

No yields were reported for this synthesis, but given the number and nature of the steps involved, the overall yield is probably quite low.

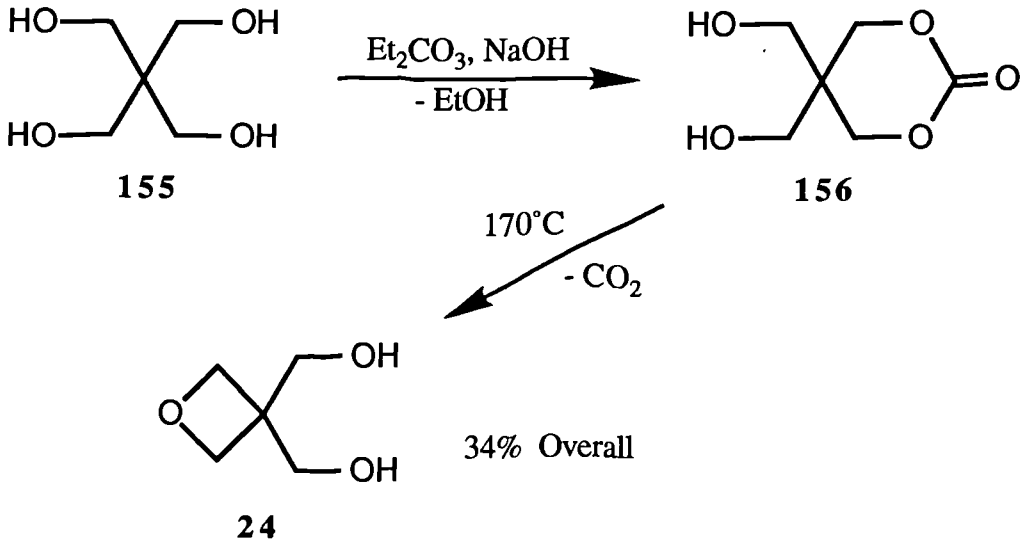
Of the three published routes to 3,3-bis(hydroxymethyl)oxetane, the Williamson reaction appears to offer the best yield. In terms of ease of preparation and cost of starting materials, however, Pattison's pyrolysis reaction is the most efficient.

The preparation of oxetane **24** was first attempted using the combined methods of Padias and Hall,[64] and Govaert and Beyaert.[13] Pentaerythritol was brominated using concentrated hydrobromic acid and acetic anhydride in acetic acid. The use of acetic acid, as a solvent, and acetic anhydride, to remove water from the mixture, cause the formation of pentaerythrityl acetate esters. After removal of the solvent, these esters were destroyed by adding hydrobromic acid and a large volume of ethanol to the crude product and distilling off the transesterification product, ethyl acetate. Bromohydrin **154** is soluble in acetonitrile but not in chloroform, and the crude product was crystallised from (9:1) chloroform / acetonitrile to give pure bromohydrin **154** in 23% yield (*cf.* Lit.[64] 65%). Cyclisation was carried out in ethanolic potassium hydroxide and gave only an 11% yield of oxetane **24**.

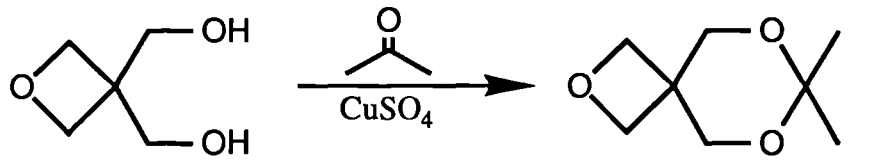


As the overall yield for these two steps was only 2.5%, a second route was tried. This was Pattison's carbonate pyrolysis method.[22]

The first attempt at forming carbonate ester **156** from pentaerythritol (**155**), using dimethyl carbonate instead of diethyl carbonate, was unsuccessful. Since the only difference between this attempted reaction and the published method was the nature of the alkyl carbonate employed, it seemed likely that it was the lower boiling point of the dimethyl carbonate (90°C) compared with that of diethyl carbonate (126°C) that was responsible for the lack of reaction. A second attempt at the reaction, this time using diethyl carbonate, gave the theoretical yield of ethanol together with a white solid product. On heating at 170°C, the solid decomposed, evolving carbon dioxide, and 3,3-bis(hydroxymethyl)oxetane distilled over and was collected as a waxy solid in 34% yield (*cf.* Lit.,[22] 34%).

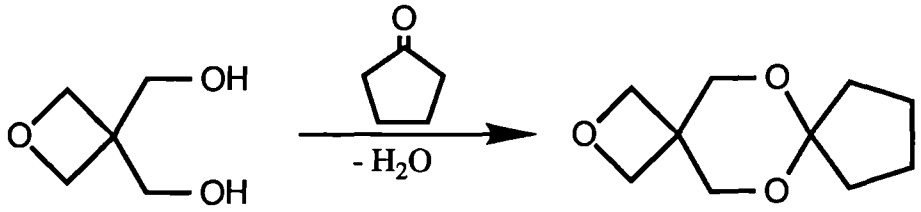


The materials obtained by these two routes had identical spectroscopic properties and two derivatives were prepared for further characterisation. The reaction of oxetane **24** with acetone in the presence of anhydrous copper (II) sulphate yielded 7,7-dimethyl-2,6,8-trioxaspiro[3.5]nonane (**160**) as a colourless oil, in good (76%) yield.



24 **160** 76%

The reaction of oxetane **24** with cyclopentanone in dry tetrahydrofuran over 4Å molecular sieve, yielded 2,6,12-trioxadispiro[3.2.4.2]tridecane (**161**) as a colourless oil, in good (90%) yield.

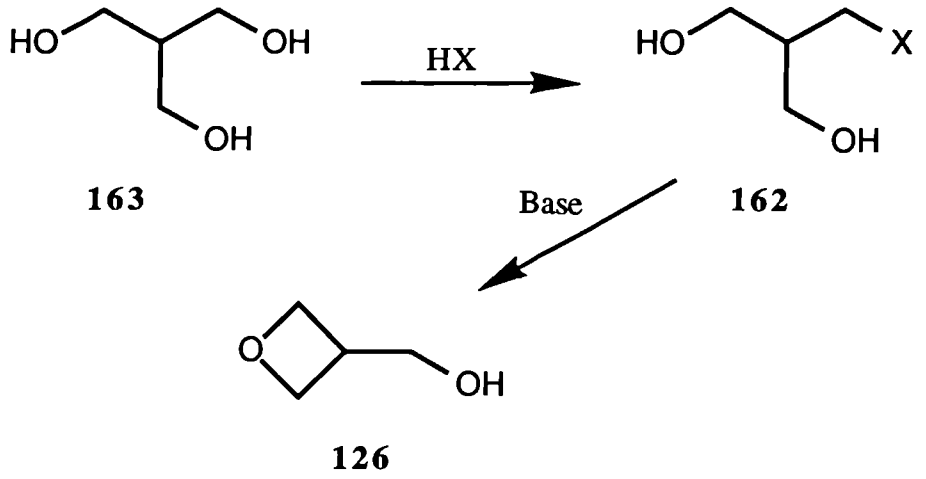


24 **161** 90%

THE SYNTHESIS OF 3-(HYDROXYMETHYL)OXETANE

3-(Hydroxymethyl)oxetane (**126**) has not previously been synthesised, and a variety of routes to this compound were therefore investigated.

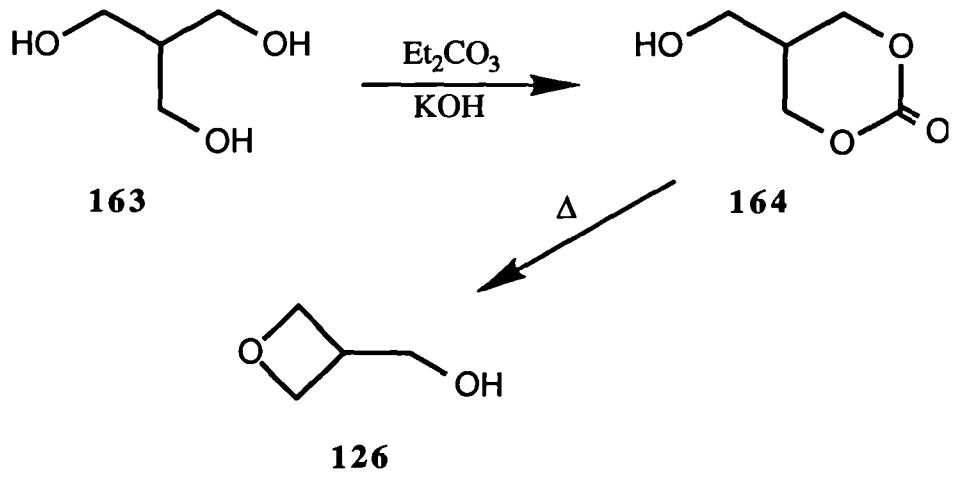
Four different strategies were considered. A Williamson ring-closure reaction would necessitate the preparation of an intermediate dihydroxy-compound **162** containing a good leaving group (X). The two most obvious routes to this intermediate are the ring-opening of a suitable oxetane, or the nucleophilic substitution of 2-(hydroxymethyl)propane-1,3-diol (**163**). Clearly the use of an oxetane precursor is not possible, since the required oxetane would be 3-(hydroxymethyl)oxetane (**126**) itself. This leaves the nucleophilic substitution of 2-(hydroxymethyl)propane-1,3-diol (**163**) with a suitable leaving group (bromide, methanesulphonate, *p*-toluenesulphonate, etc.).



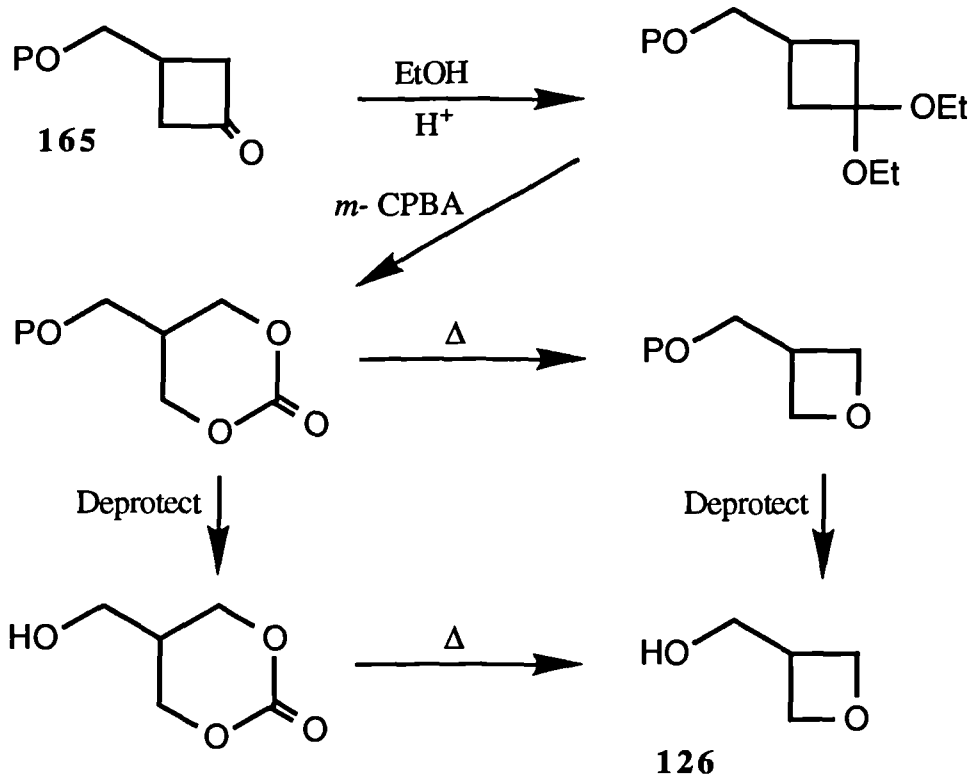
163 **162** **126**

The second strategy considered was the pyrolysis of a carbonate ester. The required ester **164** should be available from the trihydroxy-compound **163** by base-catalysed trans-esterification with diethyl carbonate, and should decompose at a fairly low temperature due to its free hydroxymethyl group (see p. 18).

A second route to cyclic carbonate esters is also of potential interest. Bailey and Shih[68] reported the conversion of acetals of 5- and 6-membered cyclic ketones into 7-



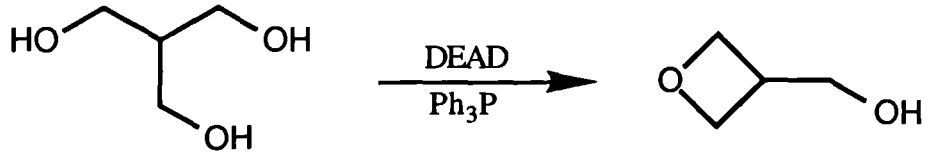
and 8-membered cyclic carbonate esters respectively. The reaction, a double Baeyer-Villiger reaction, may allow the conversion of a suitably protected cyclobutanone **165** into the required oxetane **126** by a series of simple steps (Scheme 27).



Scheme 27

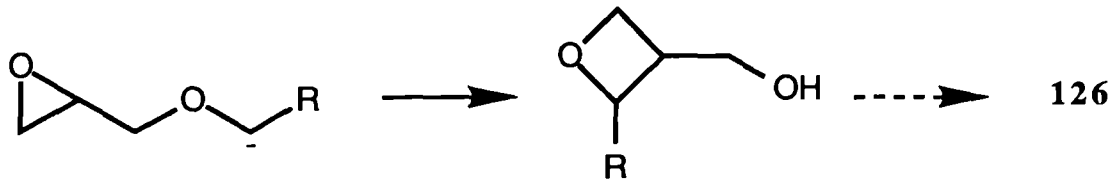
The third strategy, a Mitsunobu type ring-closure of a dihydroxy-compound

using triphenyl phosphine and diethyl azodicarboxylate to effect the dehydration, would again use triol **163** (or a suitably protected derivative) as the starting material.



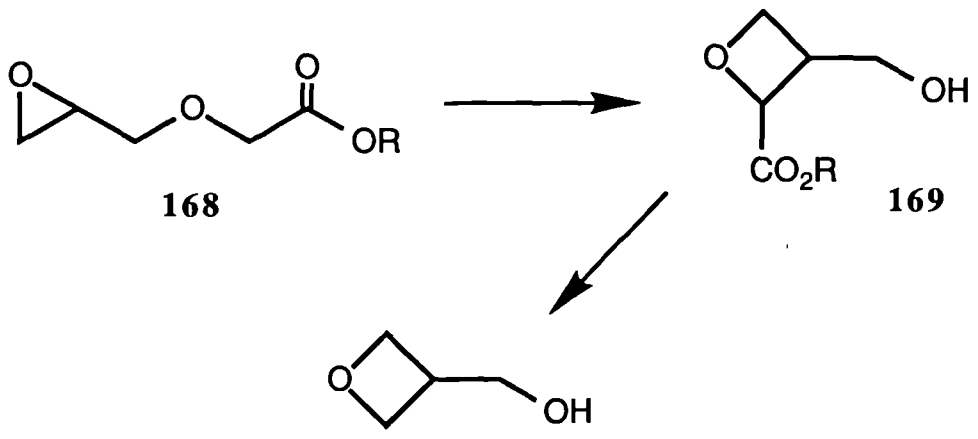
163 **126**

The fourth approach to 3-(hydroxymethyl)oxetane (**126**) involves the cyclisation of an α-glycidyloxy carbanion **166** to give oxetane **167**.



166 **167**

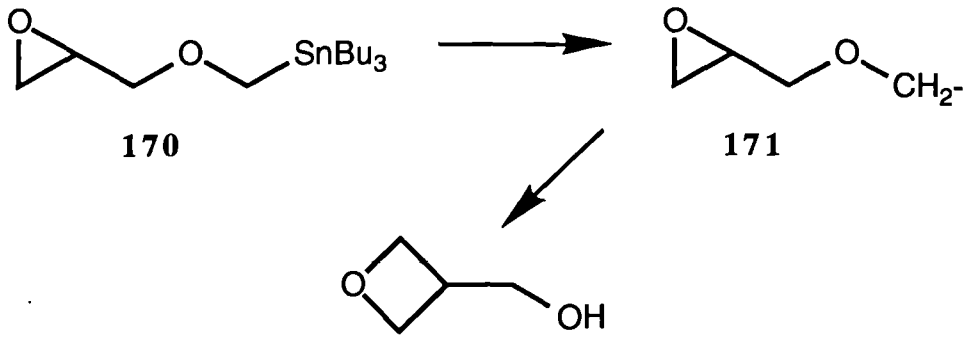
Clearly, in order to prepare the parent heterocycle, the substituent (R) must be either easily removed after the cyclisation, or be hydrogen. One useful system would be ester **168** which would give the 2-(alkoxycarbonyl)-3-(hydroxymethyl)oxetane **169**, which could then be hydrolysed and decarboxylated to give the required oxetane **126**.



168 **169**

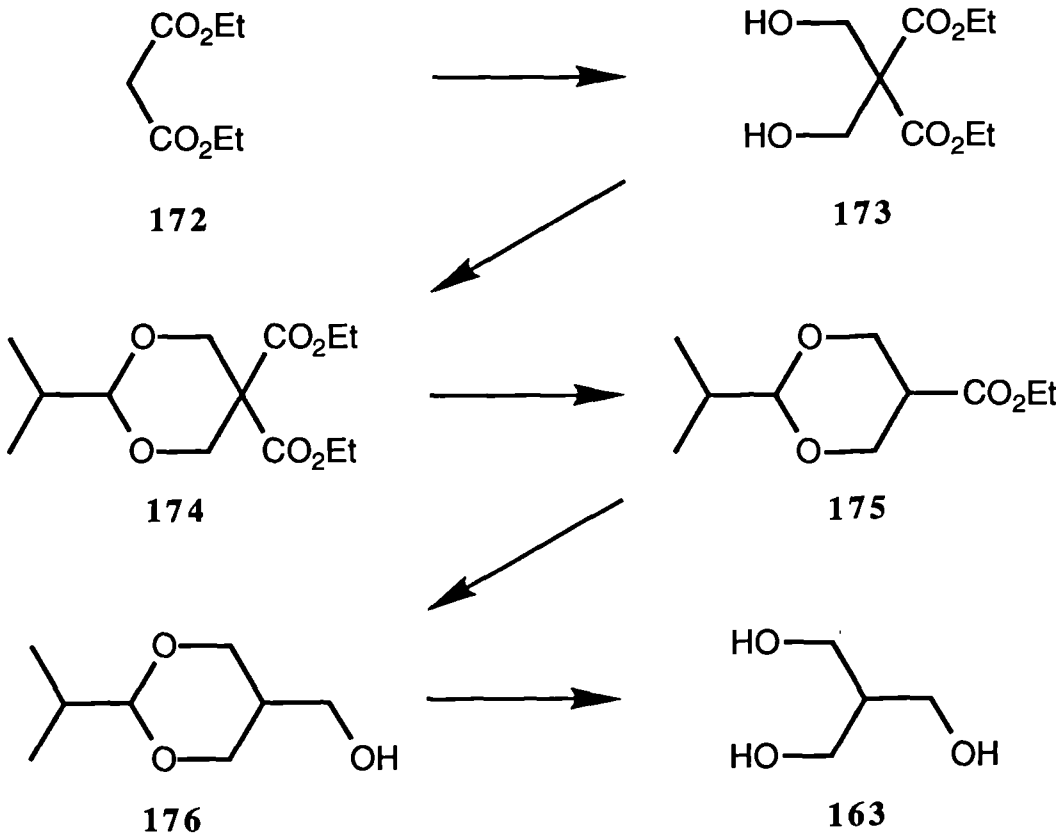
126

Alternatively the tri-*n*-butylstannane **170** which, when treated with *n*-butyllithium should give carbanion **171** would, if cyclisation occurred, give oxetane **126**.



170 **171** **126**

Clearly, the most useful precursor, and one common to three of the above strategies, is 2-(hydroxymethyl)propane-1,3-diol (**163**). This trihydroxy-compound has been synthesised in three ways.

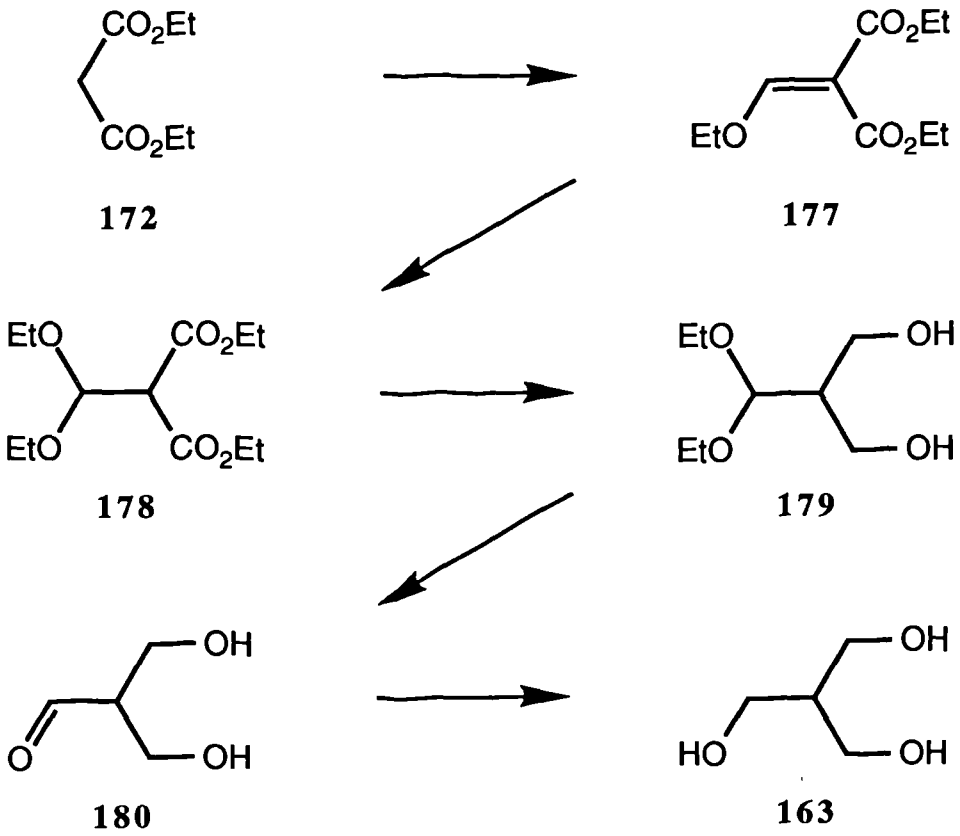


172 **173** **174** **175** **176** **163**

Scheme 28

Dekmezian and Kaloustain[69] reported a five step synthesis, starting from diethyl malonate (**172**) (see Scheme 28). The malonate ester underwent a double aldol condensation when treated with formaldehyde and base, to yield diethyl bis(hydroxymethyl)malonate (**173**). This diol reacted with isobutyraldehyde in the presence of an acid catalyst, yielding 5,5-dicarbethoxy-2-isopropyl-1,3-dioxane (**174**). The isopropylidene acetal **174** was decarboxylated using wet dimethyl sulphoxide and sodium chloride, giving 5-carbethoxy-2-isopropyl-1,3-dioxane (**175**). Reduction of ester **175** with lithium aluminium hydride afforded 5-(hydroxymethyl)-2-isopropyl-1,3-dioxane (**176**), which underwent acid hydrolysis to the required triol.

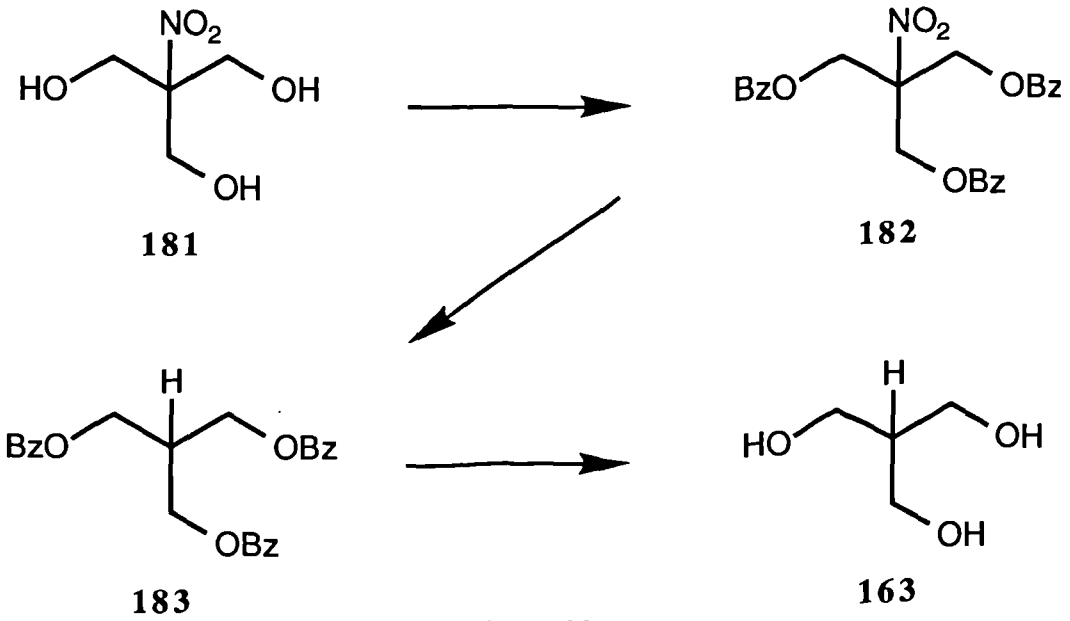
The overall yield of this synthesis was not reported but the last three steps have a combined yield of 51%.



Scheme 29

Nielsen *et al.*[70] also reported a five step synthesis from diethyl malonate (**172**)

(see Scheme 29). Treatment of the malonate ester **172** with triethyl orthoformate, acetic acid, and zinc chloride, afforded diethyl (ethoxymethylene)malonate (**177**). This enol-ether was treated with sodium ethoxide in ethanol to give diethyl (diethoxymethylene)-malonate (**178**), which was reduced to 2-(diethoxymethyl)propane-1,3-diol (**179**) using lithium aluminium hydride. Acid hydrolysis of the acetal gave the corresponding aldehyde **180** which was hydrogenated over a ruthenium on carbon catalyst to give the required alcohol, 2-(hydroxymethyl)propane-1,3-diol (**163**). The overall yield for this route is reported to be 33-46%.[70]



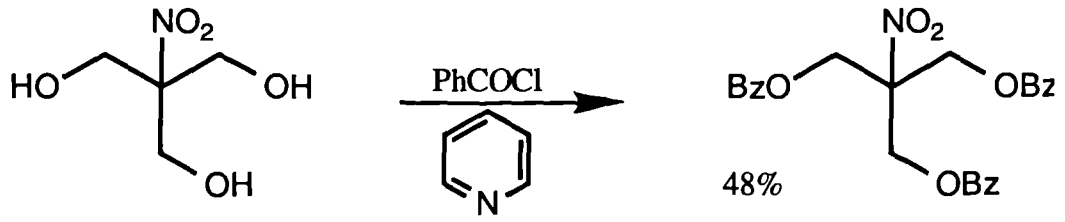
Scheme 30

The third reported synthesis, that by Latour and Wuest[71] (Scheme 30), is a three step process. 2-(Hydroxymethyl)-2-nitropropane-1,3-diol (**181**) was protected by conversion into its tribenzoate ester **182** using benzoyl chloride in pyridine. The nitro-group was removed using tri-*n*-butyltin hydride and azobis(isobutyronitrile) in benzene, to give the tribenzoate **183**. This triester was then solvolysed using sodium methoxide in methanol to give the required alcohol **163**. The overall yield of this synthesis was reported to be 70%.[71]

Of the three published routes, the third seemed the most efficient since it

combined the shortest route with the highest overall yield. All of the reagents used in this synthesis are readily available and, with the exception of tri-*n*-butyltin hydride, are relatively inexpensive.

The first attempt to prepare a sample of 2-(hydroxymethyl)propane-1,3-diol (**163**) was carried out according to the method of Latour and Wuest.[71] The protection of the three hydroxyl groups of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (**181**), using benzoyl chloride in pyridine, afforded tribenzoate ester **182** in 48% yield after re-crystallisation.

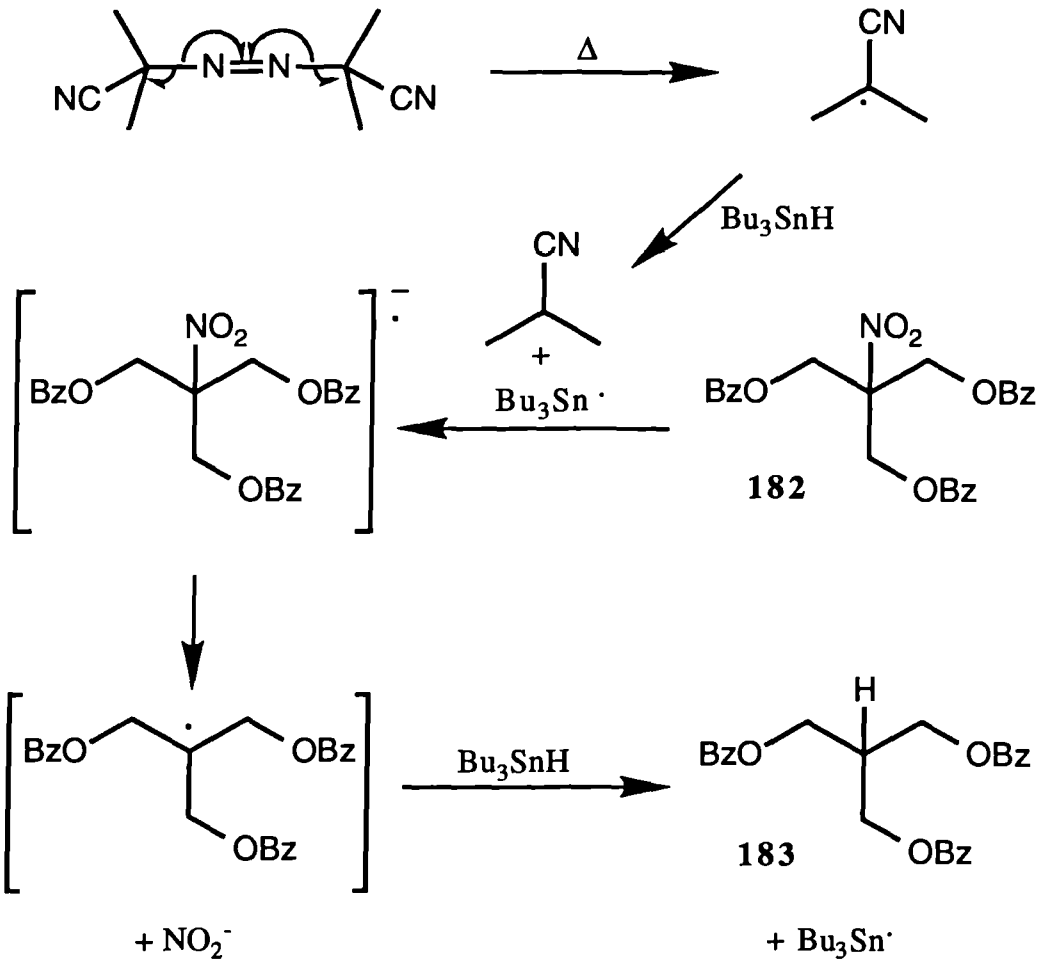


181 **182**

The second step, a radical hydro-denitration using tri-*n*-butyltin hydride in benzene, with azobis(isobutyronitrile) as initiator (see Scheme 31), was less successful. Despite the use of fresh reducing agent, recrystallised azobis(isobutyronitrile), and benzene freshly distilled from calcium hydride, the reaction consumed 3.7 equivalents of the reducing agent. The tribenzoate **183** thus produced, contained a small amount (approx. 5%) of the starting material **182** and had to be purified by flash column chromatography. Separation of the two spots on silica was difficult, and resulted on a yield of only 50%.

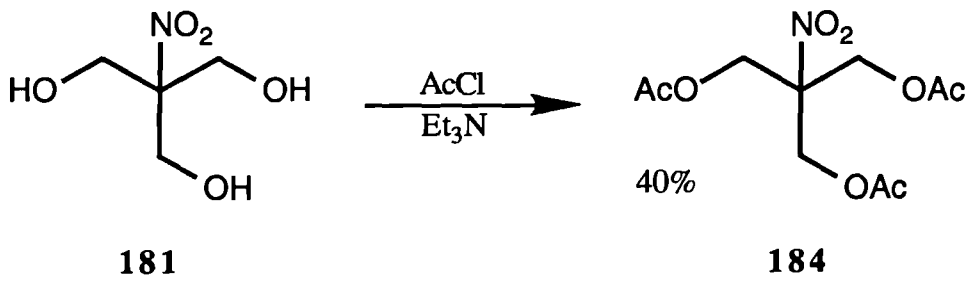
Removal of the protective benzoate ester groups was carried out using the literature method,[71] base-catalysed methanolysis. The product, a mixture of methyl benzoate, sodium hydroxide and 2-(hydroxymethyl)propane-1,3-diol (**163**) could not be separated by the reported vacuum sublimation procedure. Attempts to repeat this separation on both 100mg and 1g scales, using different types of sublimation

equipment, and at different pressures varying from 0.1 to 12 mmHg, all failed to give any product.



Scheme 31

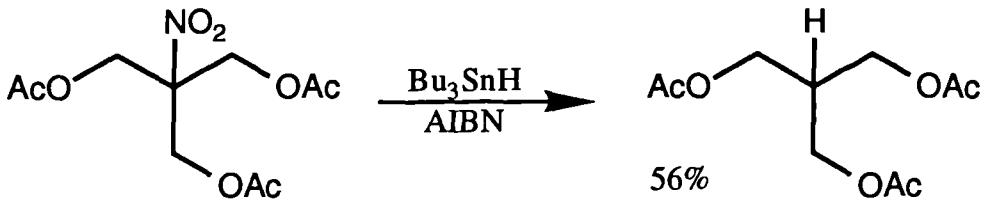
The crude product was subjected to column chromatography, but elution with methanol gave only a yellow oil from which no solid product was obtained.



181 184

A similar series of reactions based on acetate rather than benzoate esters was then carried out. The use of acetyl chloride and triethylamine in benzene to effect the esterification, allowed a much simpler work-up than that used to remove excess pyridine from the benzoylation. After purification by column chromatography, 1,3-diacetoxy-2-(acetoxymethyl)-2-nitropropane (**184**) was obtained in 40% yield.

The hydro-denitration of triacetate **184** proceeded much more smoothly than of tribenzoate **182**. The reaction was carried out as before, but in this case, only 1.9 equivalents of tri-*n*-butyltin hydride were used. After purification by column chromatography, 1,3-diacetoxy-2-(acetoxymethyl)propane (**185**) was obtained in 56% yield as a colourless oil. The decrease in the amount of reducing agent required to affect this hydro-denitration may be seen as a reflection of the decrease in hindrance of the nitro-group in triacetate **184**, compared with the corresponding tribenzoate ester **182**.

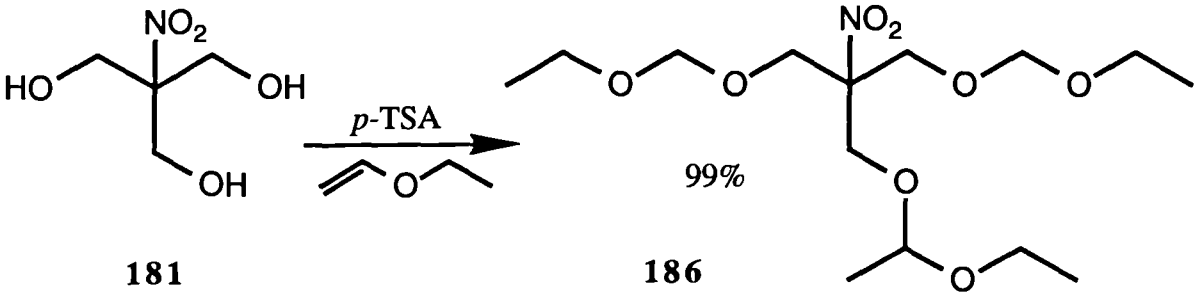


184 **185**

The base-catalysed solvolysis of ester **185** gave a viscous product containing sodium hydroxide, and again the required trihydroxy-compound **163** could not be distilled or sublimed from the mixture.

Other protective groups were then considered. 1,3-Bis-(1-ethoxyethoxy)-2-(1-ethoxyethoxymethyl)-2-nitropropane (**186**) was prepared in excellent (99%) yield by treating a suspension of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (**181**) in diethyl ether, with ethyl vinyl ether in the presence of a small amount of *p*-toluenesulphonic acid. This method was particularly convenient, since the product is highly soluble in diethyl ether and the starting material is insoluble. Hence the reaction could be

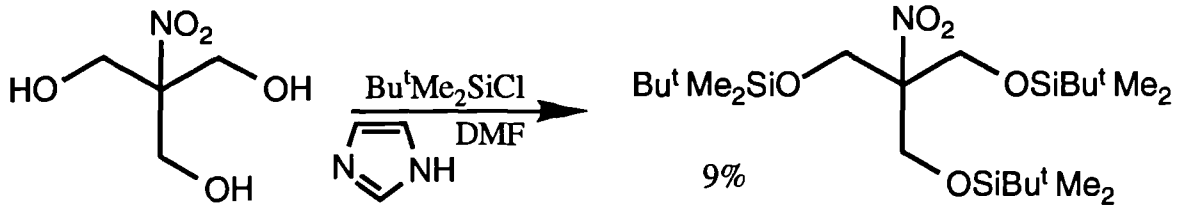
monitored visually.



181 **186**

A sample of the protected alcohol **186** was treated with tri-*n*-butyltin hydride and azobis(isobutyronitrile) in benzene. No reaction was observed under these conditions. It seems likely that the lack of reactivity is due to steric inhibition of the incoming tin radical by the three large protective groups.

A sample of 1,3-bis-(*t*-butyldimethylsilyloxy)-2-(*t*-butyldimethylsilyloxy-methyl)-2-nitropropane (**187**) was prepared by treating triol **181** with *t*-butyldimethyl-silyl chloride and imidazole in *N,N*-dimethylformamide. The product, a low melting (39-41°C) white crystalline solid, was obtained in only 9% yield.



181 **187**

The low yield of this reaction may again be due to steric inhibition of the incoming reagent by large protective groups already incorporated into the reacting molecule.

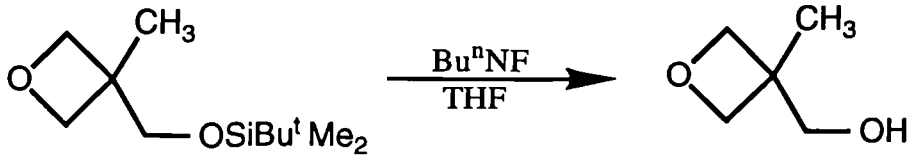
When treated with tri-*n*-butyltin hydride and azobis(isobutyronitrile) in benzene, nitro-compound **187** underwent no reaction. Again this is probably due to steric inhibition of the large tri-*n*-butyltin radical by the three large *t*-butyldimethylsilyl protective groups.

An alternative approach was clearly needed. Most of the routes to 3-(hydroxymethyl)oxetane make no use of the third hydroxyl group of triol **163**. Hence it may be advantageous to protect this site at the earliest possible opportunity (*i.e.* before hydrodenitration), and remove the protective group after cyclisation to the oxetane. This strategy should have the added advantage of increasing the solubility of many of the intermediates in aprotic solvents.

The protective group chosen must be labile under conditions for which the oxetane ring is inert. The suitability of two protective groups was investigated by using them to protect and deprotect the hydroxyl group in the commercially available 3-(hydroxymethyl)-3-methyloxetane (**122**). Firstly, the oxetane was protected as its *t*-butyldimethylsilyl ether **188** by treating it with a solution of *t*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide. The protected oxetane was obtained in excellent (97%) yield.

122 **188**

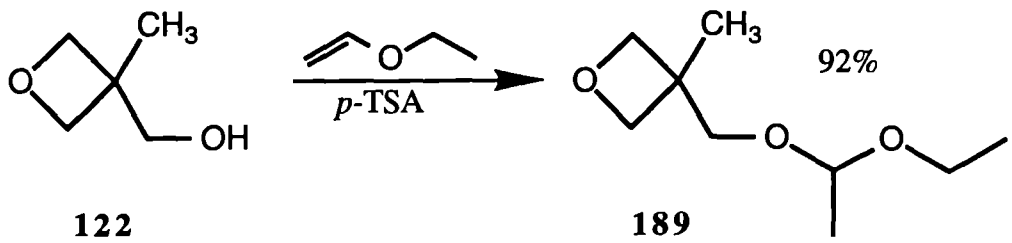
Silyl ether **188** was deprotected using tetra-*n*-butlyammonium fluoride in tetrahydrofuran, to give exclusively 3-(hydroxymethyl)-3-methyloxetane (**122**).



188 **122**

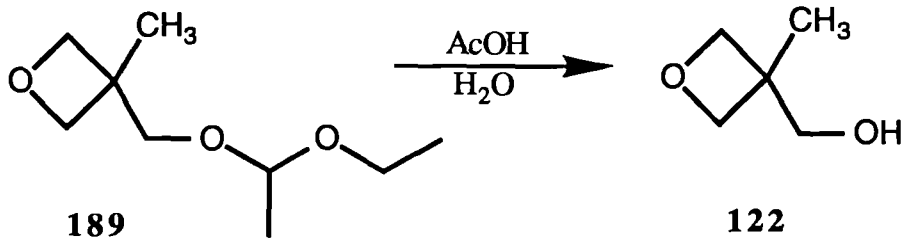
A sample of oxetane **122** was next treated with ethyl vinyl ether in the presence of

p-toluenesulphonic acid, to give a good (92%) yield of oxetane **189**.



122 **189**

When treated with dilute aqueous acetic acid, acetal **189** was hydrolysed to a mixture of compounds containing 3-(hydroxymethyl)-3-methyloxetane (**122**).



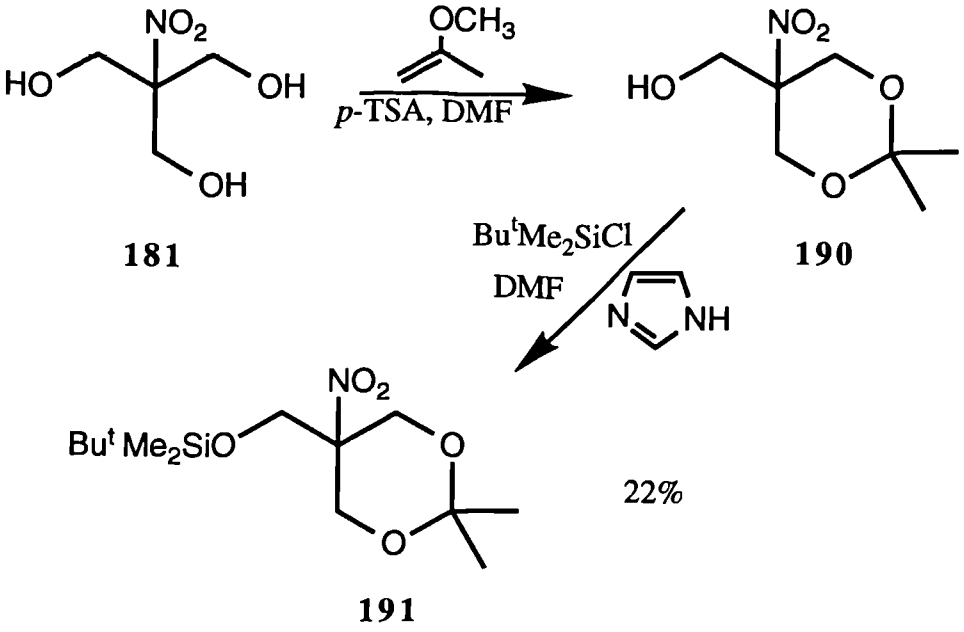
189 **122**

As the *t*-butyldimethylsilyl group offered the simplest work-up and cleanest product, it was decided to use this as the protective group.

The remaining two hydroxyl groups must also be protected before dc-nitration can take place. A convenient way to protect the two hydroxyl groups is as a cyclic acetal, formed on reaction with an aldehyde, ketone or enol ether. By forming the cyclic acetal before introducing the silyl protective group, the problem of selectively protecting the triol is overcome. A mono *t*-butyldimethylsilyl ether would have been exceptionally difficult to prepare directly, because the starting material is likely to be less soluble in most organic solvents than the mono-protected compound would be. In addition, the protection of a 1,3-dihydroxy-compound to give a 6-membered cyclic acetal is generally readily achieved, and if the reaction is carried out at sufficient dilution, no intermolecular reaction should occur.

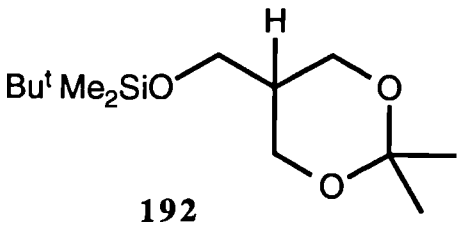
2-(Hydroxymethyl)-2-nitropropane-1,3-diol (**181**) was treated with 2-methoxy-

propene* in *N,N*-dimethylformamide and in the presence of *p*-toluenesulphonic acid catalyst. The reaction was exothermic and when it had ceased, imidazole and *t*-butyldimethylsilyl chloride were added to the mixture. The product, 5-(*t*-butyldimethylsilyloxymethyl)-2,2-dimethyl-5-nitro-1,3-dioxane (**191**) was obtained in 22% yield after separation by column chromatography.



191

The nitro-1,3-dioxane **191** was treated with tri-*n*-butyltin hydride and azobis(isobutyronitrile) in benzene, but yielded none of the expected product, 5-(*t*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxane (**192**)



192

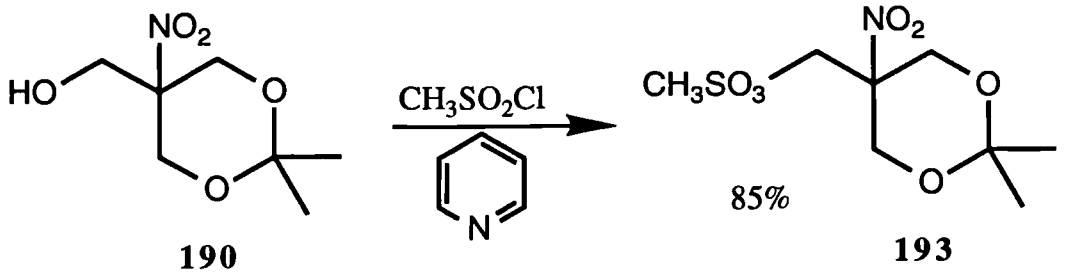
The failure of this reaction is again probably due to steric hindrance of the

* It was found to be more convenient to use this enol ether rather than acetone, which was used in the literature[80] preparation of compound **190**.

incoming tri-*n*-butyltin radical by the large *t*-butyldimethylsilyl substituent.

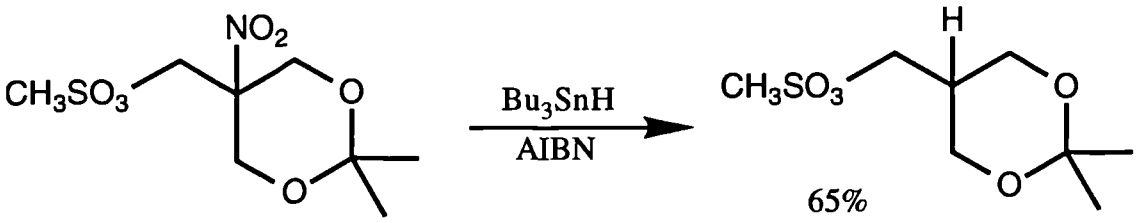
Another, and interesting variant of the present strategy was the possibility of using a good leaving group as a protective group. This eliminates the need for both protection and subsequent deprotection. The leaving group employed must be smaller than the bulky silyl group to avoid steric inhibition at the hydro-denitration step. The group chosen for this purpose was a methanesulphonate ester.

Nitro-dioxane **190** was dissolved in pyridine and treated with methanesulphonyl chloride. The product, 2,2-dimethyl-5-(methanesulphonyloxymethyl)-5-nitro-1,3-dioxane (**193**) was obtained in 85% yield after column chromatography.



190 **193**

When treated with tri-*n*-butyltin hydride and azobis(isobutyronitrile) in benzene, nitro-ester **193** was reduced to 2,2-dimethyl-5-(methanesulphonyloxymethyl)-1,3-dioxane (**194**) in moderate (65%) yield after isolation by column chromatography.

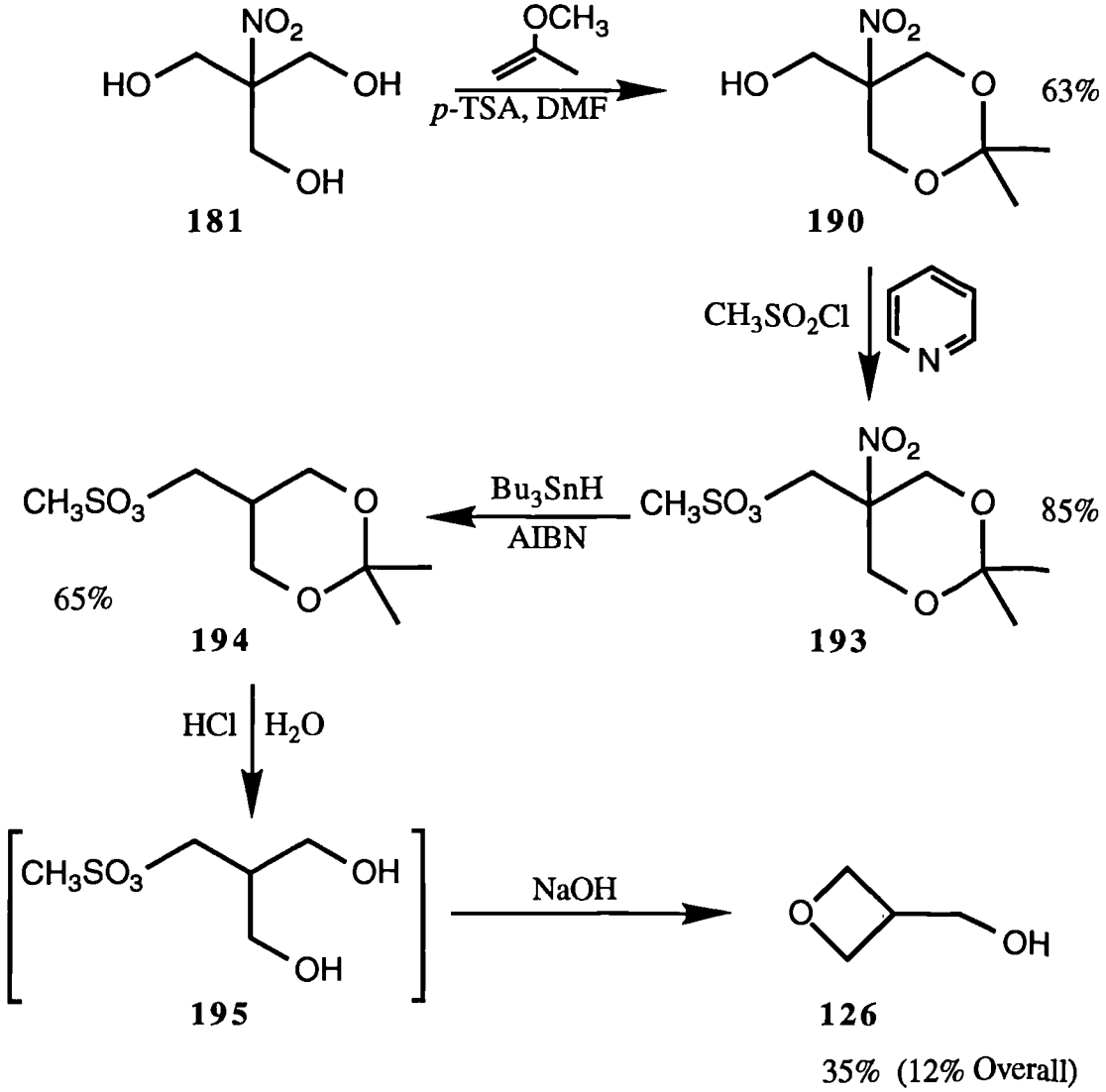


193 **194**

This compound **194** now contains the necessary leaving group, and simply needs deprotecting and treating with strong base to give 3-(hydroxymethyl)oxetane (**126**). Both of these reactions may be carried out in aqueous solution and isolation of an

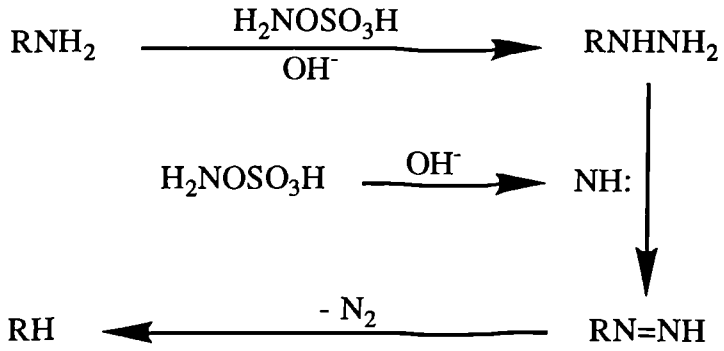
intermediate may not be necessary.

The reduced dioxane **194** was added to dilute hydrochloric acid, and after a few minutes, the insoluble heterocycle had 'dissolved'. The addition of solid sodium hydroxide to the solution, caused a violent exothermic reaction. The solution was made up to about 50% sodium hydroxide and allowed to stir for 10 minutes. Extraction of the mixture with dichloromethane and purification of the product by column chromatography gave 3-(hydroxymethyl)oxetane (**126**) in 35% yield. This synthesis, the first reported for 3-(hydroxymethyl)oxetane, has an overall yield of 12% over five steps and involves the synthesis of three intermediates (see Scheme 32).



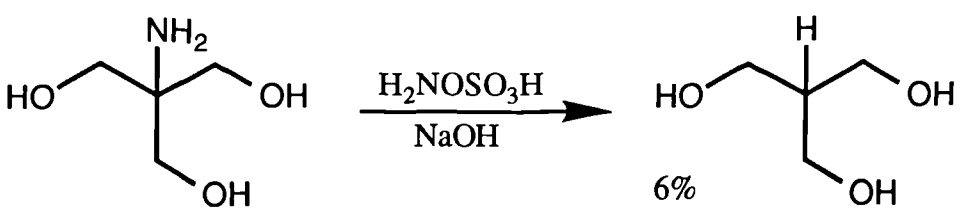
Scheme 32

The use of an expensive and toxic reagent such as tri-*n*-butyltin hydride in a large scale synthesis is impractical and undesirable. An alternative to the above route may be provided by the simple de-amination reaction reported by Doldouras and Kollonitsch.[72] This method was described as a general reaction for the conversion of a primary amine to the corresponding alkane. The following mechanism was proposed (see Scheme 33).[72]



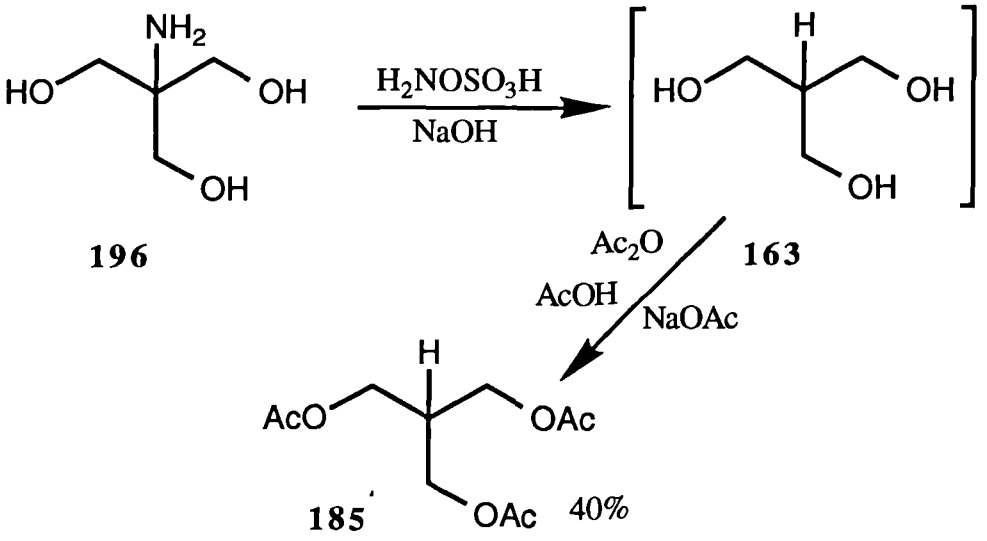
Scheme 33

Accordingly, 2-amino-2-(hydroxymethyl)propane-1,3-diol (**196**) was treated with hydroxylamine-*O*-sulphonic acid and sodium hydroxide. The product, a viscous oil, was isolated by complete evaporation of the aqueous reaction mixture and exhaustive extraction of the white solid residue with ethanol. Evaporation, followed by freezing the resulting oil in liquid nitrogen then and allowing it to warm slowly to room temperature caused solidification to occur. The solid was crystallised from acetone to yield 2-(hydroxymethyl)propane-1,3-diol (**163**) in only 6% yield. Several attempts at obtaining a higher yield of solid product failed.

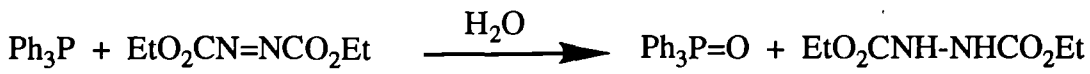


196 **163**

In an attempt to quantify the amount of 2-(hydroxymethyl)propane-1,3-diol (**163**) formed in this reaction, the crude product was acetylated using a solution of sodium acetate and acetic anhydride in acetic acid. The product 1,3-diacetoxy-2-(acetoxymethyl)propane (**185**) was obtained in 40% yield (after distillation) from the amino-triol **196**. The triacetate obtained from this reaction was identical to that prepared from the hydro-denitration of the nitro-triacetate **184** (see p. 70).



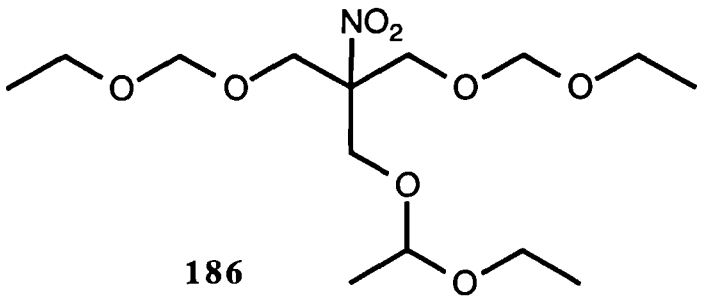
A Mitsunobu cyclo-dehydration reaction of 2-(hydroxymethyl)propane-1,3-diol (**163**) was attempted using triphenyl phosphine and diethyl azodicarboxylate. This was carried out under dilute conditions to avoid intermolecular reaction, but no significant reaction was observed. After several weeks, the formation of triphenyl phosphine oxide and 1,2-bis(ethoxycarbonyl)hydrazine, the expected bi-products of a dehydration reaction were observed (see Scheme 34).



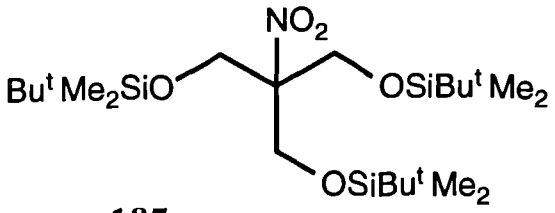
Scheme 34

The formation of bi-products may be due to the slow infiltration of water into the reaction flask. The lack of reaction of triol **163** is thought to be due to its low solubility in the reaction solvent.

The possibility of obtaining pure 2-(hydroxymethyl)propane-1,3-diol (**163**) by de-amination of a protected trihydroxy-compound was next considered. Both 1,3-bis-(*t*-butyldimethylsilyloxy)-2-(*t*-butyldimethylsilyloxymethyl)-2-nitropropane (**187**) and 1,3-bis-(1-ethoxyethoxy)-2-(1-ethoxyethoxymethyl)-2-nitropropane (**186**) were available from previous syntheses. Each of these were treated with hydrogen and a palladium on carbon catalyst. No amine was obtained from either of the molecules, even at high temperature (150°C) and pressure (200 atmospheres). This may be due to hindrance to reduction of the nitro-group by the large protective groups.

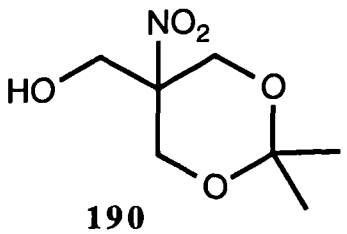


186

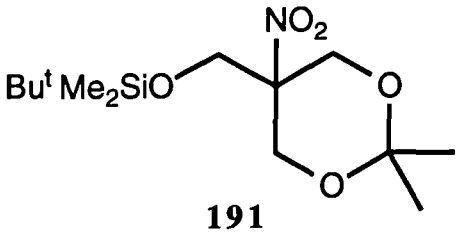


187

2,2-Dimethyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane (**190**) and its protected



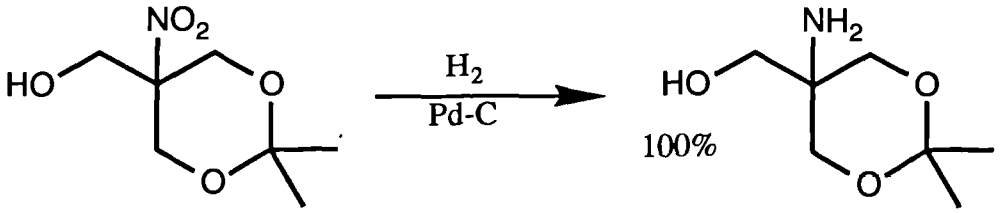
190



191

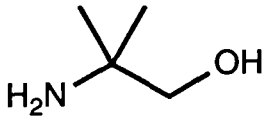
derivative, **189** were also treated with hydrogen in the presence of a catalyst.

A quantitative yield of the amino-alcohol **197** was obtained, but the protected alcohol could not be reduced.



190 **197**

The 5-amino-2,2-dimethyl-5-(hydroxymethyl)-1,3-dioxane (**197**) thus obtained was subjected to a de-amination reaction with hydroxylamine-*O*-sulphonic acid and base. However, no product was obtained from this reaction.

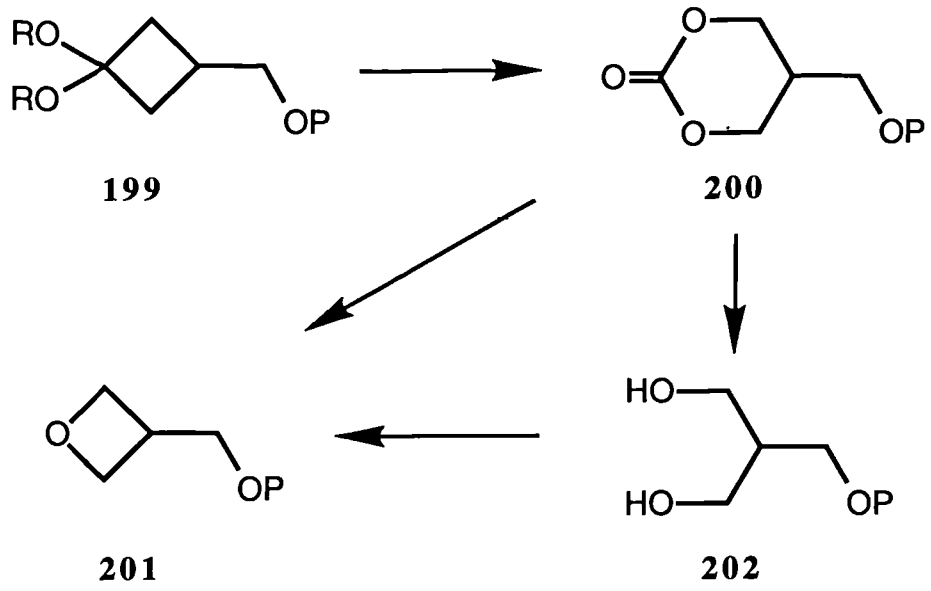


198

In order to study this de-amination, and in particular to investigate the effects of variations in the reaction conditions, the amino-alcohol **198** was used as a model compound. However, all attempts to de-aminate this compound, and also benzylamine, failed. Following this failure, the de-amination reaction was abandoned as a potential route to 3-(hydroxymethyl)oxetane precursors.

An attempt was made to prepare a cyclic carbonate ester by the method of Bailey and Shih.[68] Baeyer-Villiger oxidation of the protected cyclobutanone acetal **199** could be expected to yield the cyclic carbonate **200** (or the corresponding diethyl ortho-carbonate) which could either be pyrolysed to give an oxetane **201** or hydrolysed to the useful dihydroxy-compound **202** (see Scheme 35).

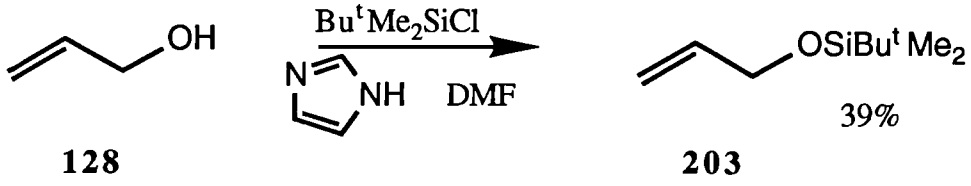
As has already been seen (p. 72), a *t*-butyldimethylsilyl ether can be removed without damage to an oxetane ring. For this reason it was chosen as the protecting group in the following synthesis.



199 **200** **202** **201**

Scheme 35

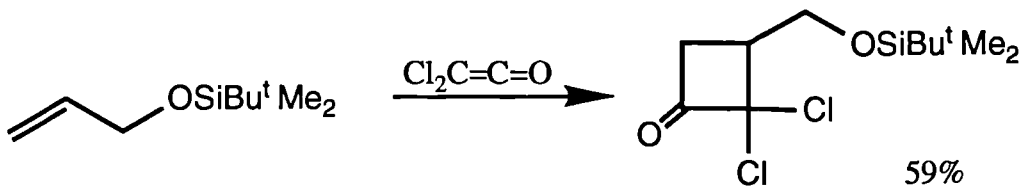
Allyl alcohol (**128**) was protected as its *t*-butyldimethylsilyl ether **203** by treating it with *t*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethyl-formamide.[57] The product was obtained in 39% yield.



128 **203**

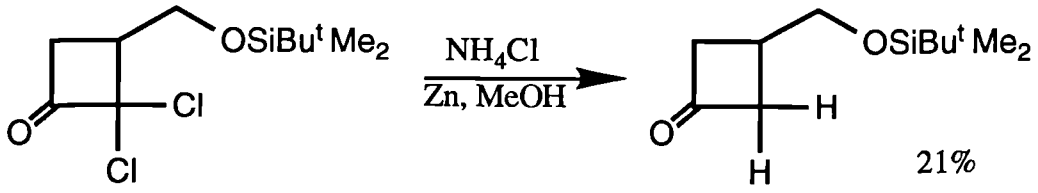
The reaction of alkenes with dichloroketene was shown to give 2,2-dichlorocyclobutanones in good yield with high regioselectivity. A monosubstituted alkene usually gives a 3-substituted 2,2-dichlorocyclobutanone.[73,74]

Dichloroketene was generated *in situ* by the method of Hassner[74] and it reacted with the allyl silyl ether **203** to give a single regio-isomer **204** in 59% yield after



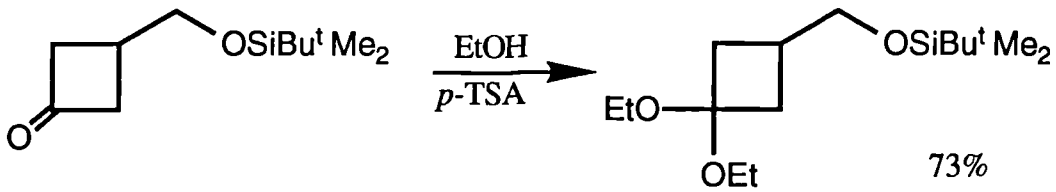
203 **204**

purification by flash chromatography. Chloro-compound **204** was reduced to ketone **205** by the action of zinc and ammonium chloride in methanol.[75] The ketone was obtained in 21% yield after purification by column chromatography.



204 **205**

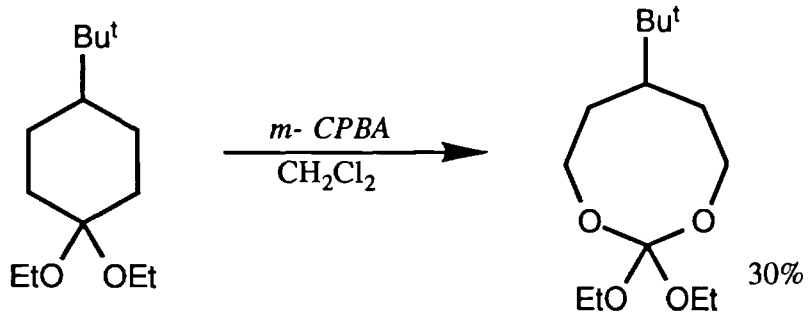
In order to carry out the Baeyer-Villiger oxidation,[68] the ketone must be converted into its diethyl acetal **206**. This acetal was obtained by treating the parent ketone **205** with *p*-toluenesulphonic acid in ethanol. A yield of 73% was obtained after purification by column chromatography.



205 **206**

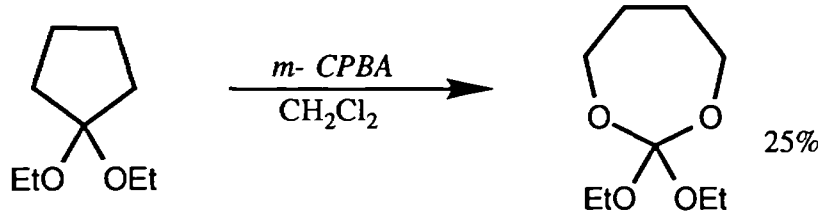
When the diethyl acetal **206** thus obtained was treated with *m*-chloro-peroxybenzoic acid in dichloromethane, no reaction took place. This result is somewhat surprising, as the diethyl acetal **207** of a cyclohexanone readily reacted with two

equivalents of *m*-chloroperoxybenzoic acid to give an 8-membered cyclic orthocarbonate ester **208**.[68] The yield for this oxidation was 30%.



207 **208**

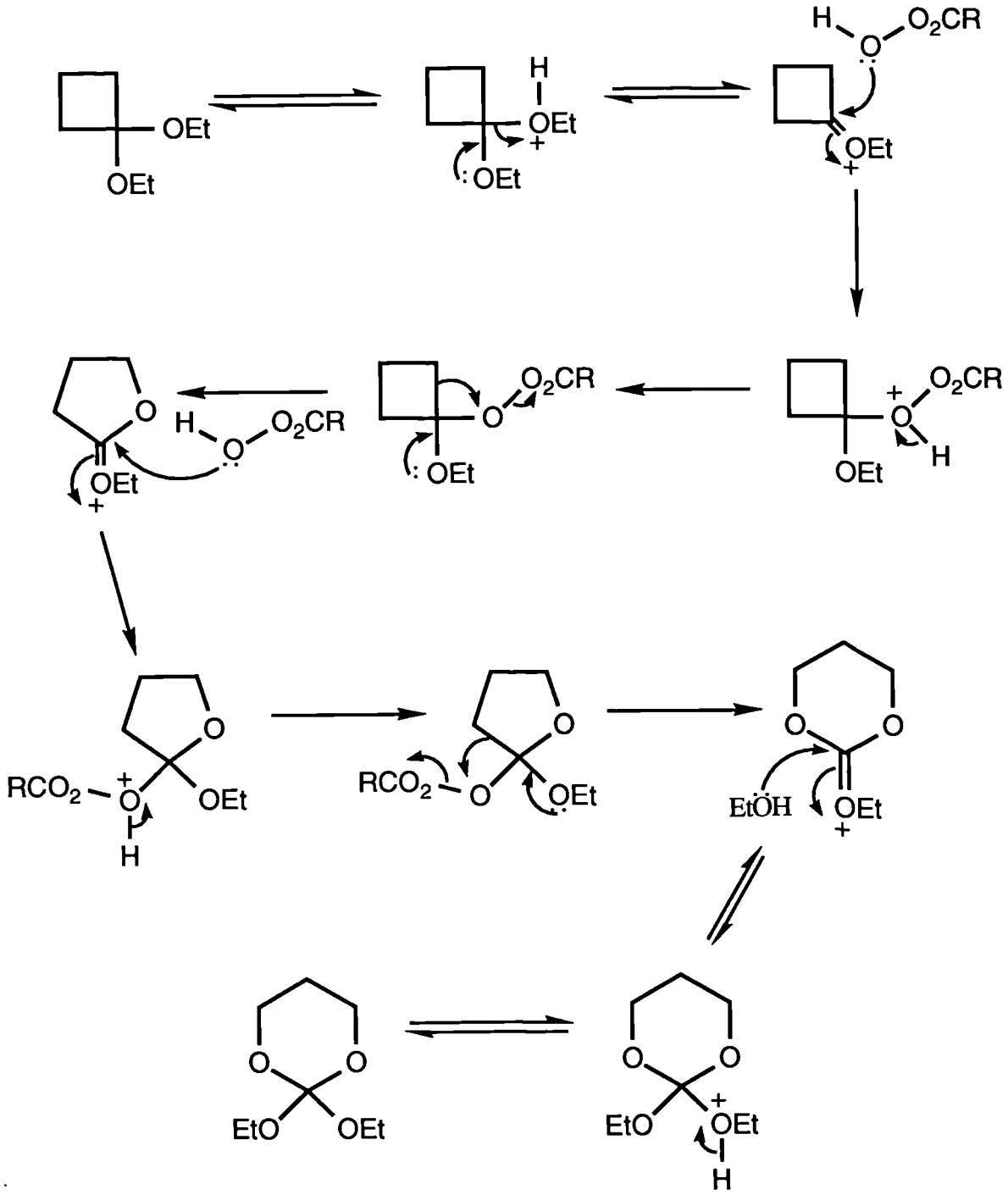
In a similar reaction, the oxidation of diethyl acetal **209** of cyclopentanone gave the 7-membered orthocarbonate ester **210** in only 25% yield.[68]



209 **210**

The 4-membered analogue used in our reaction may be seen as a continuation of this series, indicating that the decrease in yield is due to steric rather than electronic considerations. The most likely mechanism for this reaction (see Scheme 36) involves the formation and subsequent reaction of an exocyclic double-bond. Energetically, this presents no problem in a 6-membered ring, and in a 5-membered ring only a small increase in ring-strain would result. However, in the case of a 4-membered ring, the formation of an exocyclic double-bond would cause a significant increase in ring-strain. The trend in the observed yields for reactions using these systems, 30%, 25% and 0%

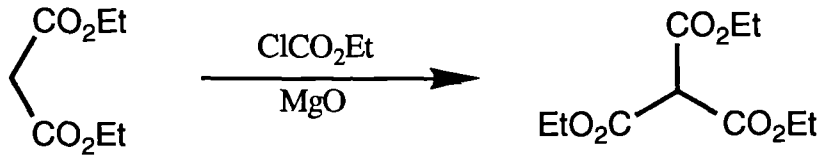
respectively, is in line with the proposed reaction mechanism.



Scheme 36

One other attempt was made to prepare 2-(hydroxymethyl)propane-1,3-diol (**163**) and its derivatives. Triethyl methanetricarboxylate (**211**) was prepared from

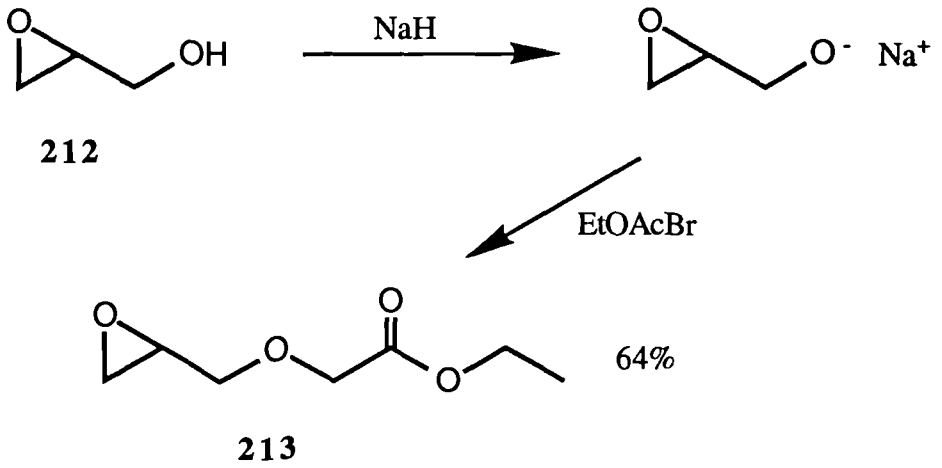
diethyl malonate (**172**) using the method of Skarzewski.[76] The tricarboxylic ester was obtained in 44% yield using the magnesium oxide mediated condensation of diethyl malonate with ethyl chloroformate. It was later discovered that such tri-esters could not be reduced to the corresponding trihydroxy-compounds,[77] and so no further investigation was undertaken.



172 **211**

The remaining strategy, the cyclisation of an α-glycidyloxy carbanion, was attempted using the two types of epoxide outlined earlier (p. 64).

A glycidyloxy ester was prepared by treating glycidol (**212**) with sodium hydride, and adding ethyl bromoacetate. The product, ethyl glycidyloxyacetate (**213**), was obtained in 64% yield after purification by column chromatography.

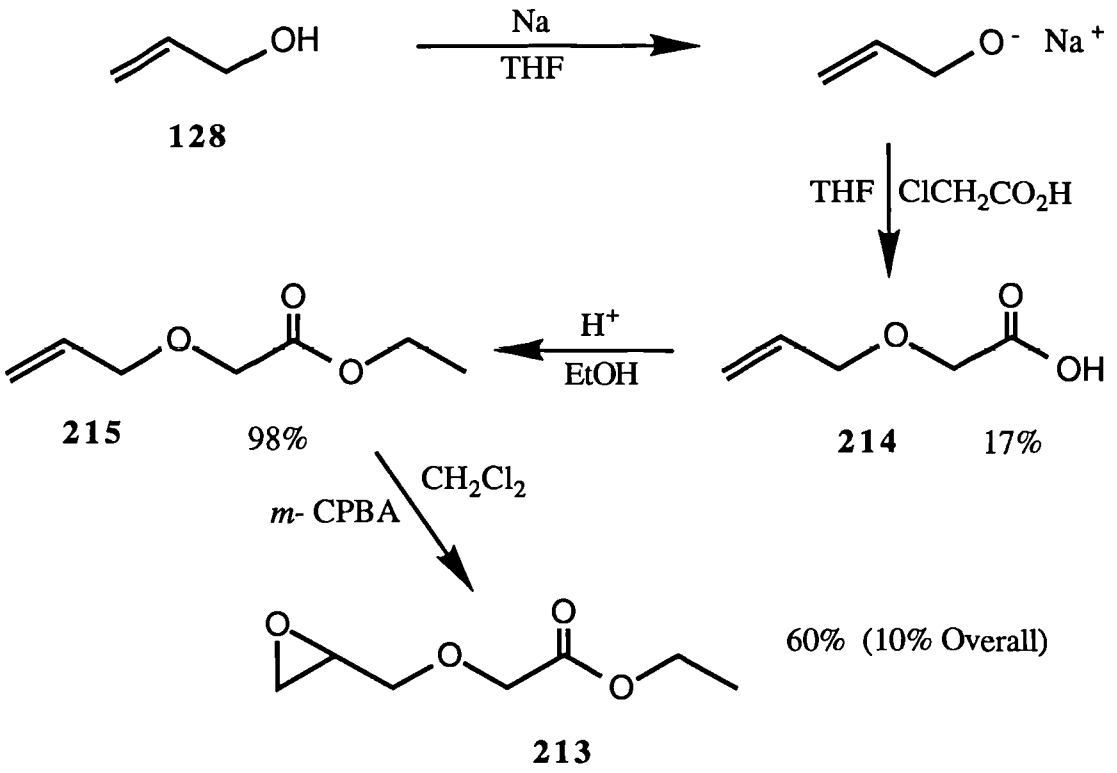


212

213

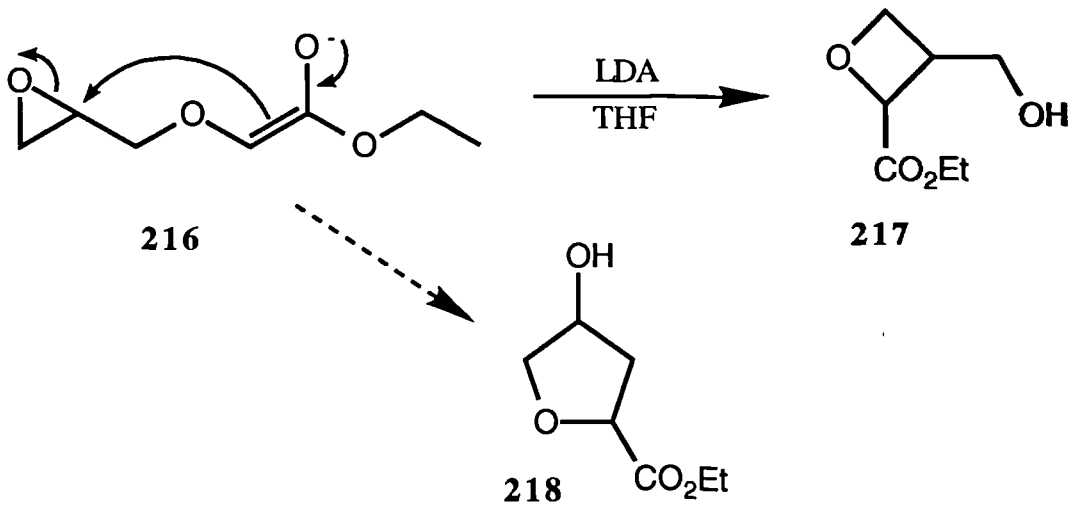
An identical sample was prepared by treating allyl alcohol (**128**) with sodium and adding chloroacetic acid. The resulting allyloxyacetic acid (**214**) was esterified using ethanol and acid to give ethyl allyloxyacetate (**215**). Epoxidation of the alkene **215**

afforded ethyl glycidyloxyacetate (**213**) in an overall yield of only 10%.

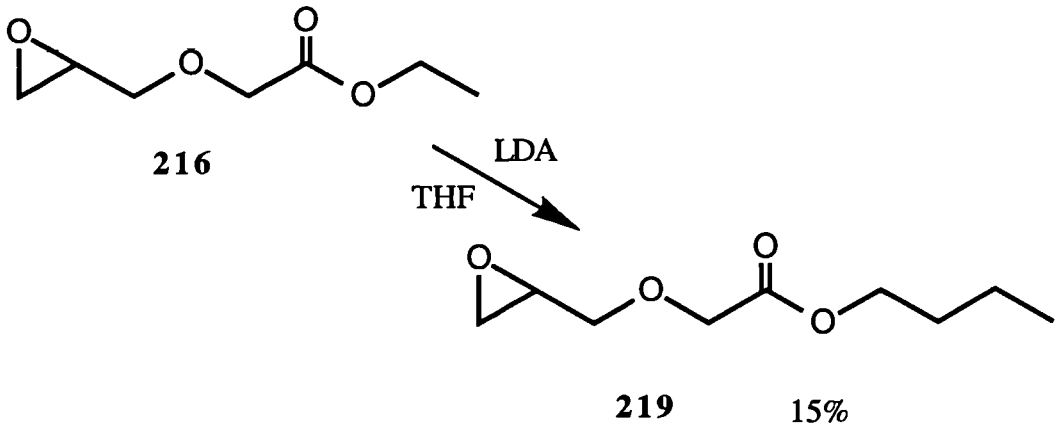


Scheme 37

Deprotonation of this compound using lithium di-isopropylamide in tetrahydrofuran, to give anion **216** might be be expected to give oxetane **217** or perhaps furanol **218.**

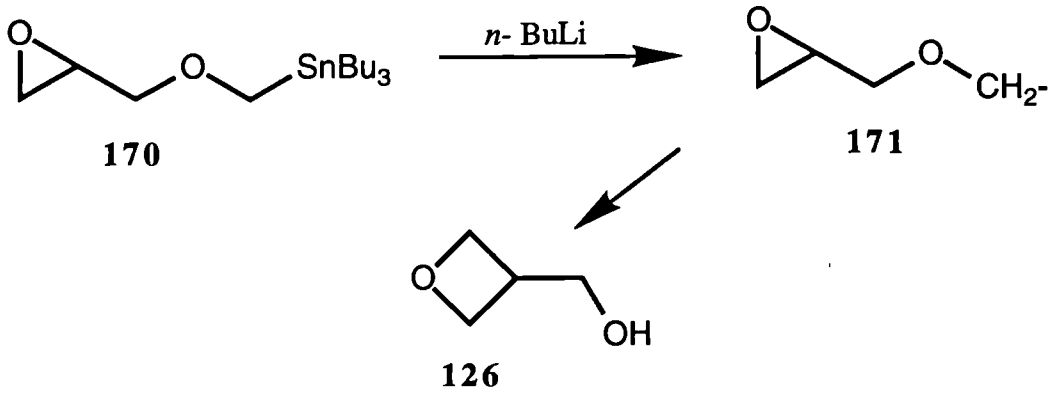


However, no oxetane **217** was obtained, and after a prolonged period at room temperature, a modest (15%) yield of a new ester was isolated. This product was identified as *n*-butyl glycidyloxyacetate (**219**). It presumably arises from the reaction of butoxide present in the *n*-butyllithium used to generate the lithium di-isopropylamide for use in this reaction.



216 **219** 15%

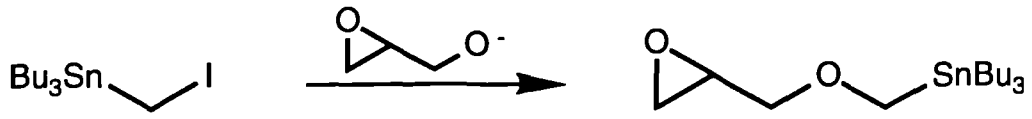
Several attempts were made to effect cyclisation, but none were successful. A more nucleophilic anion was clearly needed. The simple, discrete carbanion **171** is ideal as it gives the desired product, 3-(hydroxymethyl)oxetane (**126**), in a single step. It might be prepared by a simple metal exchange reaction from its tri-*n*-butyltin derivative **170**.



170 **171** **126**

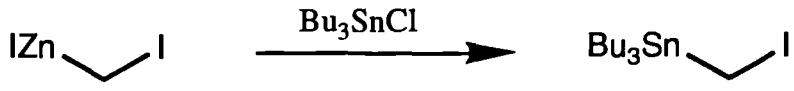
The most obvious preparation of a tin compound such as epoxide **170** is the

method reported by Still.[78] Treating a solution of (iodomethyl)tri-*n*-butyl tin (**220**) with glycidyloxy anion should give the ether **170**.



220 **170**

The intermediate **220** may be generated by the action of (iodomethyl)zinc iodide (**221**) on tri-*n*-butyltin chloride.[78]



221 **220**

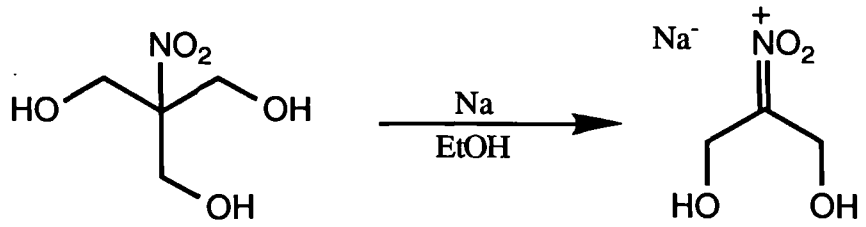
Intermediate **221** is itself available[79] by reaction of di-iodomethane with activated zinc. This highly reactive reagent must be kept in solution and used rapidly.

Using the combined methods of Seyferth[79] and Still,[78] (iodomethyl)zinc iodide (**221**) was prepared and was then treated with tri-*n*-butyltin chloride. However, this product, on treatment with glycidyloxy anion failed to give the glycidyl ether **170**.

MISCELLANEOUS REACTIONS

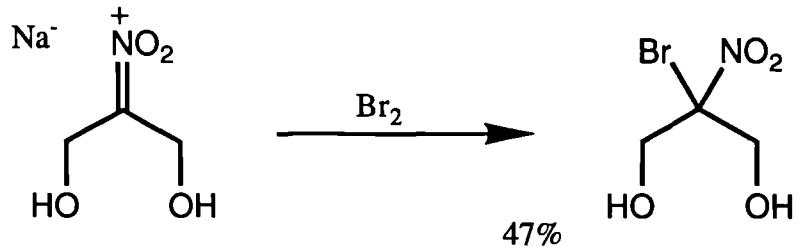
It was found during an attempt to prepare a carbonate ester of the nitro-triol **181**, that treatment with strong base caused a retro-aldol reaction. This reaction was investigated further, since it could provide a useful route to 2-nitroglycidol (**224**) and its derivatives.

Nitronate **222**, a white solid, was obtained in good yield by treating triol **181** with one equivalent of sodium in ethanol.



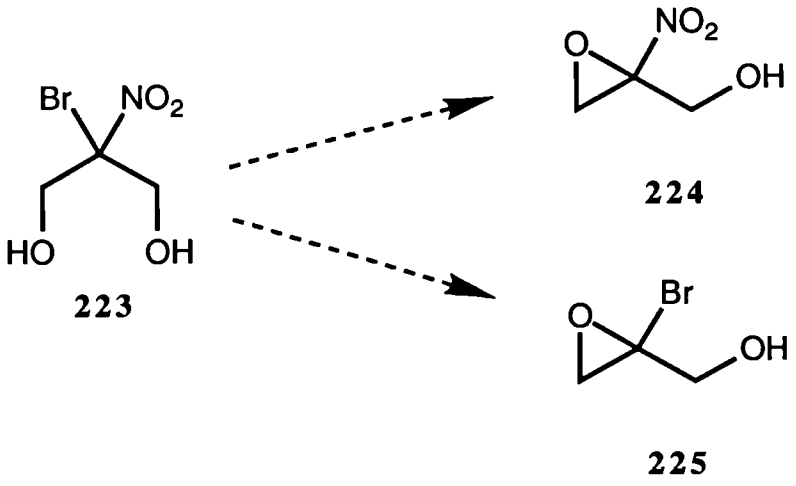
181 **222**

The nitronate **222** on bromination gave 2-bromo-2-nitropropane-1,3-diol (**223**) in 47% yield.



222 **223**

This, on treatment with ethanolic potassium hydroxide yielded an orange glass (completely insoluble in any common solvent), rather than the expected nitro-epoxide **224** or even the bromo-compound **225**.



Clearly, the potential for formation of a highly cross-linked polymer is high due to the presence of two good leaving groups and two hydroxyl groups. The orange glass is probably such a polymer.

CONCLUSIONS

The synthesis of 3-hydroxyoxetane, previously reported by Baum *et al.* (see p. 48),[55] has been improved. Incorporation of the following six changes has increased the overall yield of the synthesis from 30% to 45% (pp. 49-54).

(i) The use of epibromohydrin rather than the corresponding chloro-compound.

(ii) Isolation of the ring-opened product by flash column chromatography.

(iii) The use of freshly distilled ethyl vinyl ether to protect the hydroxyl group.

(iv) Isolation of the protected alcohol by flash column chromatography.

(v) The use of aqueous acetic acid, rather than methanolic *p*-toluenesulphonic acid, to deprotect the cyclised product.

(vi) Isolation of the final product by flash column chromatography.

The syntheses of 3-nitrato-oxetane and poly-3-nitrato-oxetane have been achieved for the first time. The nitrate ester was prepared from 3-hydroxyoxetane using a solution of dinitrogen pentaoxide in dichloromethane. The polymer produced had an average molecular mass of 1640, and a glass transition temperature of approximately -23°C. Although this temperature is too high for the polymer itself to be of use as an energetic binder, co-polymers may have much lower glass transition temperatures and hence be of great interest.

The one-pot synthesis of 3,3-bis(hydroxymethyl)oxetane previously reported by Pattison[22] (see p. 57) has been found to give a moderate yield (p. 60). Despite the inherent side-reactions associated with this type of reaction (p. 18), the nature and inexpense of the starting material and reagents employed make this a relatively efficient method for the synthesis of the oxetane. There seems little scope to improve the efficiency of this synthesis.

3-(Hydroxymethyl)oxetane has been prepared for the first time (see p. 76). The synthesis involves five steps from 2-(hydroxymethyl)-2-nitropropane-1,3-diol, and requires the isolation of three intermediates (pp. 73-6). The overall yield, 12%, leaves room for further improvement, particularly in the deprotection and cyclisation steps which have a combined yield of only 35%.

2-(Hydroxymethyl)propane-1,3-diol has been prepared in one step from 2-amino-2-(hydroxymethyl)propane-1,3-diol by the action of hydroxylamine-*O*-sulphonic acid and aqueous base (see p.78). Difficulties in the isolation of this product have resulted in a yield of only 6%. Acetylation of the crude product however, results in a 40% yield of the corresponding triacetate (p. 79).

EXPERIMENTAL

FOREWORD TO EXPERIMENTAL

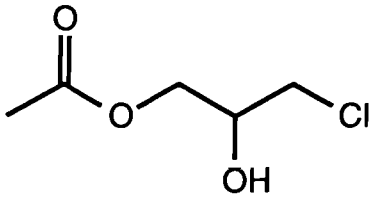
Infrared absorption spectra were determined for nujol mulls or liquid films on a Perkin-Elmer 1700 FT-IR spectrophotometer. Proton magnetic resonance (p.m.r.) spectra were recorded for solutions in deuteriochloroform on a Bruker AC-300 (300MHz) spectrometer or on a Perkin-Elmer R32 (90MHz) spectrometer and referenced to tetramethylsilane ($\delta = 0.0$). The following abbreviations have been used to describe the signals observed:-

s	=	singlet
d	=	doublet
t	=	triplet
q	=	quartet
m	=	multiplet
bs	=	broad singlet

Low resolution mass spectra were determined by ammonia chemical ionisation (C.I.) on a Finnegan 4000 instrument. High resolution mass spectra were determined by ammonia C.I. on a Kratos "Concept" instrument by the Greater Manchester Mass Spectrometry Service at the University of Manchester. Thin layer chromatography (t.l.c.) was carried out using Camlab 0.25 mm silica plates which were visualised using basic potassium permanganate solution or an ethanolic solution of either vanillin or phosphomolybdic acid. Flash chromatography was carried out using Merck 'Kieselgel 60' (0.040-0.063mm) silica, approximately 50 g silica per 1 g sample. Solvents were dried before use, and the extracts in organic solvents were dried over exsiccated magnesium sulphate before being evaporated under reduced pressure on a rotary evaporator.

THE PREPARATION OF 3-HYDROXYOXETANE AND RELATED COMPOUNDS

3-Chloro-2-hydroxypropyl acetate (**140**)



140

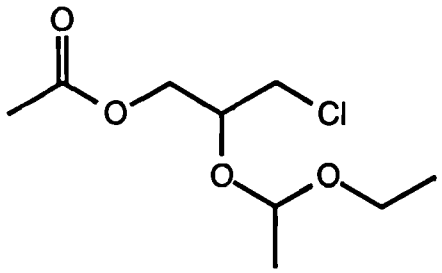
To a solution of iron (III) chloride (60 mg) in glacial acetic acid (24.5 g, 400 mmol) in a 250 ml. round-bottomed flask fitted with a reflux condenser, was added epichlorohydrin (37.0 g, 400 mmol) dropwise with magnetic stirring. When addition was complete (approx. 10 min.), the resulting solution was heated at 70°C for 24 h. and then distilled under reduced pressure to give 3-chloro-2-hydroxypropyl acetate (34.9 g, 57%) as a yellow oil, b.p. 80-82°C / 1 mmHg.

υ_{max} 3432 (OH), 1735 and 1244 cm^{-1} (acetate).

δ_H 2.09 (s, 3H, $C\underline{H}_3$), 2.6 (bs, 1H, O$\underline{H}$), 3.5-3.7 (m, 2H, $CHC\underline{H}_2Cl$), 4.05 (m, 1H, $CH_2C\underline{H}(OH)CH_2$) and 4.18 (d, 2H, $CHC\underline{H}_2OH$).

M/Z 170 (M+18).

3-Chloro-2-(1-ethoxyethoxy)propyl acetate (**141**)



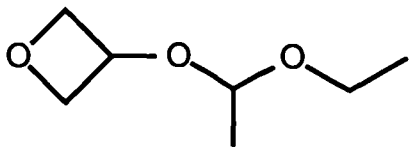
141

A mixture of *p*-toluenesulphonic acid (1.0 g) and 3-chloro-2-hydroxypropyl acetate (61.0 g, 500 mmol) was magnetically stirred at 0°C in a 250 ml. round-bottomed flask fitted with a reflux condenser. Freshly distilled ethyl vinyl ether (76.6 g, 500 mmol) was added at a rate such that the temperature remained below 30°C (ice / water cooling) and the mixture was stirred at 35°C for a further 24 h. After neutralising with solid sodium hydrogen carbonate (450 mg), the crude product was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (4:1) yielded 3-chloro-2-(1-ethoxyethoxy)propyl acetate (45.1 g, 201 mmol, 40%) as a yellow oil.

υ_{max} 1745 and 1235 cm^{-1} (acetate).

δ_H 1.17 (t, 3H, CH_2CH_3), 1.32 (m, 3H, $CHC\underline{H}_3$), 2.03 (s, 3H, $O_2CC\underline{H}_3$), 3.4-3.8 (m, 4H, $CH_3C\underline{H}_2O$ and $CHC\underline{H}_2Cl$), 3.9-4.3 (m, 3H, $CH_3CO_2C\underline{H}_2C\underline{H}(OR)CH_2$), and 4.82 (m, 1H, $OC\underline{H}(CH_3)O$).

3-(1-Ethoxyethoxy)oxetane (**142**)



142

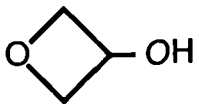
A magnetically-stirred solution of sodium hydroxide (8.8 g, 220 mmol) in water (8.8 ml) in a 100 ml. round-bottomed flask, was heated under reflux and 3-chloro-2-(1-ethoxyethoxy)propyl acetate (19.0 g, 84.6 mmol) was added dropwise. When addition was complete (approx. 90 min) the mixture was heated under reflux for a further 4 h. then cooled and diluted with water (100 ml). The solution was extracted with dichloromethane (100, 2 x 50 ml) and the combined extract was dried and evaporated. Distillation of the residue gave 3-(1-ethoxyethoxy)oxetane (4.4 g, 36%) as a colourless oil, b.p. 153-5°C / 760 mmHg.

υ_{max} 980 and 934 cm^{-1} (oxetane ring).

δ_H 1.1 (t, 3H, $CH_2C\underline{H}_3$), 1.2 (d, 3H, $CHC\underline{H}_3$), 3.4-3.6 (m, 3H, $CH_3C\underline{H}_2O$ and oxetane H-3), and 4.6-4.8 (m, 5H, oxetane H-$2_{\alpha+\beta}$, H-$4_{\alpha+\beta}$ and $OC\underline{H}(CH_3)O$).

M/Z 164 (M+18).

3-Hydroxyoxetane (**127**)



127

(a) A solution of 3-(1-ethoxyethoxy)oxetane (4.5 g, 30 mmol) in glacial acetic acid (4 ml) and water (10 ml) in a 50 ml. round-bottomed flask was magnetically stirred for

60 min. at room temperature. The mixture was neutralised with solid sodium hydrogen carbonate (5.6 g) and the product was added to ethyl acetate (250 ml). The solution was dried and evaporated, and the residue was column chromatographed. Elution with light petroleum (b.p 40-60°C) / ethyl acetate (4:1) gave 3-hydroxyoxetane (1.2 g, 54%) as a colourless oil b.p. 63-5°C / 1 mmHg.

υ_{max} 3400 (OH), and 964 cm^{-1} (oxetane ring).

δ_H 3.7 (bs, 1H, O<u>H</u>), 4.5 (m, 2H, H-2_β and H-4_β), and 4.8 (m, 3H, H-2_α, H-3_β and H-4_α).

M/Z 92 (M+18).

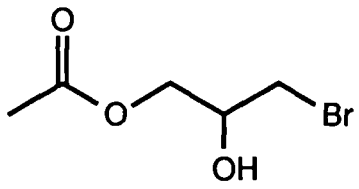
(b) A magnetically-stirred solution of sodium hydroxide (7.5 g, 19 mmol) in water (7.5 ml) was heated under reflux in a 50 ml. round-bottomed flask, and 3-bromo-2-(1-ethoxyethoxy)propyl acetate (16.0 g, 60 mmol) was added dropwise over a period of 90 min. The mixture was heated at reflux for a further 4 h., then diluted with water (100 ml) and the mixture was extracted with dichloromethane (100, 2 x 50 ml), and the combined extract was evaporated. The residue was dissolved in a mixture of glacial acetic acid (1.0 g) and water (9.0 g) and the solution was heated at 50°C for 30 min. The reaction mixture was neutralised with sodium hydrogen carbonate (1.4 g) and the whole was added to ethyl acetate (100 ml), and the product was dried and evaporated. The residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (4:1) gave 3-hydroxyoxetane (2.6 g, 59%) as a colourless oil.

υ_{max} 3370 (OH), and 970 cm^{-1} (oxetane ring).

δ_H 3.7 (bs, 1H, O<u>H</u>), 4.5 (m, 2H, H-2_α and H-4_α), and 4.8 (m, 3H, H-2_β, H-3_α and H-4_β).

M/Z 92 (M+18).

3-Bromo-2-hydroxypropyl acetate (144)



144

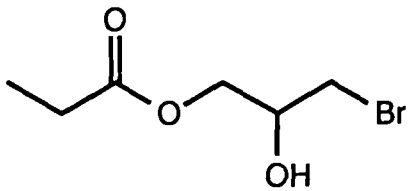
To a magnetically-stirred solution of iron (III) chloride (300 mg) in glacial acetic acid (6.0 g, 100 mmol) in a 50 ml. round-bottomed flask, was added epibromohydrin (13.7 g, 100 mmol) at a rate such that the temperature remained at approximately 60°C. The resulting red-brown solution was stirred at room temperature for 24 h. Ethyl acetate (100 ml) was added and the solution was washed successively with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The solution was dried and evaporated, and the residue was column chromatographed. Elution with light petroleum (b.p 40-60°C) / ethyl acetate (4:1) gave 3-bromo-2-hydroxypropyl acetate (17.1 g, 87%) as a yellow oil.

υ_{max} 3435 (OH), and 1737 cm^{-1} (ester).

δ_H 2.0 (s, 3H, $C\underline{H}_3$), 3.5 (m, 2H, $C\underline{H}_2Br$), and 4.1-4.3 (m, 3H, $CO_2C\underline{H}_2C\underline{H}OH$).

M/Z 214 and 216 (M+18).

3-Bromo-2-hydroxypropyl propanoate (146, R = CH_3CH_2)



To a magnetically-stirred solution of iron (III) chloride (120 mg) in propionic acid (2.98 g, 40 mmol) in a 25 ml. round-bottomed flask, was added epibromohydrin

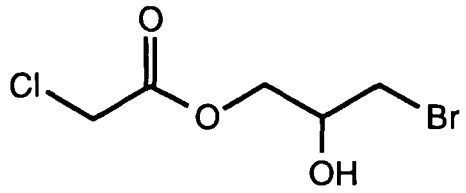
(5.50 g, 40 mmol) at a rate such that the temperature remained at approximately 60°C. The resulting red-brown solution was stirred at room temperature for 24 h. Ethyl acetate (40 ml) was added and the solution was washed successively with saturated aqueous sodium hydrogen carbonate (20 ml) and water (20 ml). The solution was dried and evaporated, and the residue was column chromatographed. Elution with light petroleum (b.p 40-60°C) / ethyl acetate (4:1) gave 3-bromo-2-hydroxypropyl propanoate (4.50 g, 61%) as a yellow oil.

υ_{max} 3448 (OH), and 1736 cm^{-1} (ester).

δ_H 1.13 (t, 3H, $CH_2C\underline{H}_3$), 2.36 (q, 2H, $C\underline{H}_2CH_3$), 2.6 (bs, 1H, O<u>H</u>), 3.46 (m, 2H, $C\underline{H}_2Br$), 4.04 (m, 1H, $CH_2C\underline{H}(OH)CH_2$), and 4.20 (d, 2H, CH_2O_2C).

M/Z 228 and 230 (M+18).

<u>3-Bromo-2'-chloro-2-hydroxypropyl acetate (**146**, R = CH_2Cl)</u>



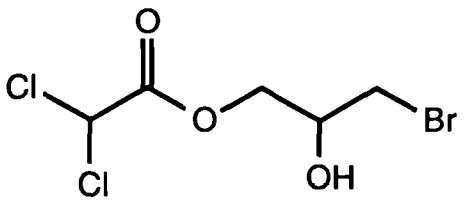
To a magnetically-stirred solution of iron (III) chloride (60 mg) in epibromohydrin (2.75 g, 20 mmol) in a 10 ml. round-bottomed flask, was added chloroacetic acid (1.90 g, 20 mmol) portionwise. The resulting (brown) solution was stirred at room temperature for 24 h. Ethyl acetate (20 ml) was added and the solution was washed successively with saturated aqueous sodium hydrogen carbonate (10 ml) and water (10 ml). The solution was dried and evaporated, and the residue was column chromatographed. Elution with light petroleum (b.p 40-60°C) / ethyl acetate (4:1) gave 3-bromo-2'-chloro-2-hydroxypropyl acetate (3.80 g, 82%) as a light brown oil.

υ_{max} 3457 (OH), and 1736 cm^{-1} (ester).

δ_H 2.0 (s, 2H), and 2.8-4.6 (m, 5H).

M/Z 248, 250, and 252 (M+18).

3-Bromo-2',2'-dichloro-2-hydroxypropyl acetate (**146**, R = $CHCl_2$)



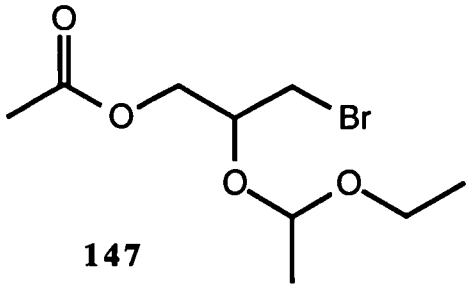
To a magnetically-stirred solution of iron (III) chloride (60 mg) in dichloroacetic acid (2.58 g, 20 mmol) in a 10 ml. round-bottomed flask, was added epibromohydrin (2.75 g, 20 mmol) dropwise. The resulting (brown) solution was stirred at room temperature for 24 h. Ethyl acetate (20 ml) was added and the solution was washed successively with saturated aqueous sodium hydrogen carbonate (10 ml) and water (10 ml). The solution was dried and evaporated, and the residue was column chromatographed. Elution with light petroleum (b.p 40-60°C) / ethyl acetate (4:1) gave 3-bromo-2',2'-dichloro-2-hydroxypropyl acetate (3.40 g, 64%) as a pale brown oil.

υ_{max} 3468 (OH), and 1741 cm^{-1} (ester).

δ_H 2.0 (s, 1H), and 3.3-4.4 (m, 5H).

M/Z 282, 284, 286, and 288 (M+18).

3-Bromo-2-(1-ethoxyethoxy)propyl acetate (**147**)



147

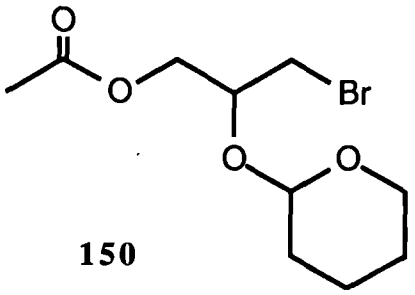
To a magnetically-stirred solution of *p*-toluenesulphonic acid (50 mg) in 3-bromo-2-hydroxypropyl acetate (1.97 g, 10 mmol) in a 10 ml. round-bottomed flask fitted with a reflux condenser, was added ethyl vinyl ether* (1.08 g, 15 mmol) dropwise, at a rate such that the temperature remained below 40°C (ice / water cooling). When addition was complete (approx. 20 min) the reaction mixture was stirred for a further 1 h., when solid sodium hydrogen carbonate (25 mg) was added. The whole was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave 3-bromo-2-(1-ethoxyethoxy)propyl acetate (2.30 g, 87% yield) as a colourless oil.

* Ethyl vinyl ether was freshly distilled from sodium before use.

υ_{max} 1743 cm^{-1} (ester).

δ_H 1.15 (t, 3H, $CH_2C\underline{H}_3$), 1.3 (m, 3H, $CHC\underline{H}_3$), 2.00 (s, 3H, CH_3CO_2), 3.4-3.7 (m, 4H, $CH_3C\underline{H}_2O$ and $C\underline{H}_2Br$), 4.0 (m, 1H, $CH_2C\underline{H}(OR)CH_2$), 4.2 (m, 2H, $C\underline{H}_2O_2CCH_3$), and 4.8 (m, 1H, $OC\underline{H}(CH_3)O$).

3-Bromo-2-(2-tetrahydropyranyloxy)propyl acetate (**150**)



150

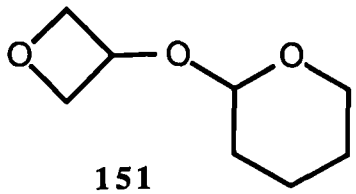
To a magnetically-stirred solution of 3-bromo-2-hydroxypropyl acetate (19.7 g, 100 mmol) and *p*-toluenesulphonic acid (100 mg) in dichloromethane (25 ml), in a 100 ml round-bottomed flask and under an argon atmosphere, was added 2,3-dihydropyran (10.0 g, 115 mmol) dropwise over a period of 5 min. After stirring for 30 min. the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (2 x 25 ml) and with water (25 ml). The solution was then dried and evaporated, and the residue was column chromatographed. Elution with light petroleum (b.p 40-60°C) / ethyl acetate (8:1) gave 3-bromo-2-(tetrahydropyranyloxy)propyl acetate (18.3 g, 65 mmol, 65%) as a pale yellow oil.

υ_{max} 815 (tetrahydropyran), and 1746 cm^{-1} (acetate ester).

δ_H 1.5-1.8 (m, 6H, tetrahydropyranyl ring), 2.0 (s, 3H, $C\underline{H}_3CO_2$), 3.5 (m, 2H, ring $C\underline{H}_2O$), 4.1-4.3 (m, 2H, $C\underline{H}_2Br$), 4.6-4.8 (m, 2H, $C\underline{H}_2OAc$), 4.9 (t, 1H, acetal C<u>H</u>), and 5.1 (m, 1H, $CH_2C\underline{H}(OR)CH_2$).

M/Z 281 and 283 (M+1), and 299 and 300 (M+18).

3-(2-Tetrahydropyranyloxy)oxetane (**151**)



151

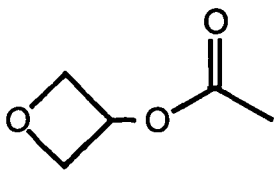
To a magnetically-stirred solution of sodium hydroxide (5.0 g, 125 mmol) in water (5 ml) heated under reflux in a 25 ml round-bottomed flask fitted with a reflux condenser and an addition funnel, was added 3-bromo-2-(2-tetrahydropyranyl)propyl acetate (5.9 g, 21 mmol) dropwise over a period of 5 min. The mixture was heated at reflux for 4 h., then dissolved in water (50 ml) and the resulting solution was extracted with diethyl ether (3 x 50 ml). The combined extract was dried and evaporated and the crude product was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (16:1) gave 3-(2-tetrahydropyranyloxy)oxetane (1.2 g, 6.4 mmol, 30%), as a colourless oil.

υ_{max} 815 (tetrahydropyran), and 982 and 1035 cm^{-1} (oxetane).

δ_H 1.4-1.8 (m, 6H, tetrahydropyran ring), 3.7 (m, 2H tetrahydropyran ring), 4.4 (m, 2H, oxetane H-2α and H-4α), 4.5 (m, 1H, OC<u>H</u>(R)O), and 4.6 (m, 3H, H-2β, H-3α and H-4β).

M/Z 159 (M+1), and 176 (M+18).

3-Acetoxyoxetane (**152**)



152

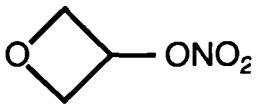
A solution of 3-hydroxyoxetane (40 mg, 0.54 mmol) and triethylamine (56 mg, 0.55 mmol) in benzene (1.0 ml) in a 5 ml. round-bottomed flask was cooled to 0°C. Acetyl chloride (43 mg, 0.55 mmol) was added dropwise and with magnetic stirring at a rate such that the temperature remained at 0°C (ice / salt cooling) and when addition was complete (approx. 5 min), the mixture was stirred for a further 40 min. The product was added to water (5 ml) and the mixture was extracted with ethyl acetate (3 x 5 ml). The combined extract was dried and evaporated to give crude 3-acetoxyoxetane (53 mg, 74%) as a yellow oil.

υ_{max} 1747 and 1256 cm^{-1} (acetate).

δ_H 2.05 (s, 3H, acetate), 4.6 (m, 2H, H-2α and H-4α), 4.9 (m, 2H, H-2β and H-4β) and 5.4 (m, 1H, H-3α).

M/Z 117 (M+1), and 136 (M+18).

3-Nitrato-oxetane (**123**)



123

To a magnetically-stirred solution of 3-hydroxyoxetane (193 mg, 2.61 mmol) in dichloromethane (2 ml) in a 10 ml round-bottomed flask, at -78°C was added dropwise

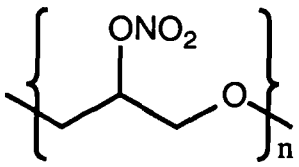
a solution of dinitrogen pentaoxide (285 mg, 2.63 mmol) in dichloromethane (2 ml). When addition was complete (approx. 5 min), the solution was allowed to stir for a further 5 min. The solution was then diluted with dichloromethane (20 ml), and the solution was poured into 10% aqueous sodium bicarbonate (20 ml). The organic layer was washed with water (20 ml) and dried. Evaporation of the solvent yielded crude 3-nitratooxetane (165 mg, 53%) as a colourless oil.

υ_{max} 977 (oxetane), and 1279 and 1639 cm^{-1} (nitrate ester).

δ_H 4.6 (m, 2H, H-2_α and H-4_α), 4.9 (m, 2H, H-2_β and H-4_β), and 5.6 (m, 1H, H-3_α).

δ_C 74 and 75 (C-2 and C-4), and 80 (C-3).

poly-3-Nitrato-oxetane (**153**)



153

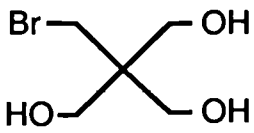
To a magnetically-stirred solution of boron trifluoride etherate (1.09 g, 7.71 mmol) in glycerol (0.355 g, 3.85 mmol) in a 200 ml jacketed reaction vessel at 15.0°C under a nitrogen atmosphere, was added a solution of 3-nitrato-oxetane (6.88 g, 58 mmol) in dichloromethane (100 ml) dropwise over a period of 15 h. The product was allowed to stir for a further 4 h. before being quenched with water (20 ml) and the mixture was stirred for 20 min. It was then poured into saturated aqueous sodium hydrogen carbonate (200 ml) and the whole was stirred for 20 min. before being separated. The organic layer was washed with water (100 ml), then dried and evaporated to give *poly*-3-nitratooxetane (6.9 g, 95%), as a pale yellow oil.

Mass average 1640.

Tg -22.7°C.

THE PREPARATION OF 3,3-BIS(HYDROXYMETHYL)OXETANE AND RELATED COMPOUNDS

2-(Bromomethyl)-2-(hydroxymethyl)propane-1,3-diol (154)



154

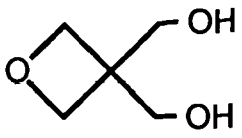
A mixture of pentaerythritol (20.0 g, 147 mmol), 48% hydrobromic acid (1.6 ml, 9.5 mmol) and glacial acetic acid (50 ml) in a 250 ml. round-bottomed flask was heated under reflux until it became homogenous (approx. 20 min). 48% Hydrobromic acid (17.0 ml, 100 mmol) and acetic anhydride (31.0 ml) were added and refluxing was continued for 3 h. After a further addition of 48% hydrobromic acid (9.4 ml, 56 mmol) and acetic anhydride (15.0 ml), heating was continued for a further 4 h. Most of the acetic acid was evaporated under reduced pressure, and ethanol (75 ml) and 48% hydrobromic acid (1.7 ml, 10 mmol) were added to the residue. Slow distillation through a 1 m. Vigreux column yielded a mixture of ethanol and ethyl acetate and when 43 ml. had been obtained, further ethanol (75 ml) was added and the distillation was continued until a further 130 ml. was obtained. The solvent was then completely evaporated under reduced pressure, and water (100 ml) was added to the residue. The aqueous phase was washed with carbon tetrachloride (2 x 100 ml) and diethyl ether (2 x 100 ml) before being evaporated. The residue was crystallised from a mixture (9:1) of chloroform and acetonitrile (100 ml), and gave 2-(bromomethyl)-2-(hydroxymethyl)propane-1,3-diol (7.3 g, 23.1%) as white needles m.p. 75-76°C (Lit.,[63] 75-76°C).

υ_{max} 3200 cm^{-1} (OH).

δ_H 2.1 (t, 3H, O<u>H</u>), 3.50 (s, 2H, C<u>H</u>$_2$Br), and 3.73 (d, 6H, C<u>H</u>$_2$OH).

M/Z 199 and 201 (M+1), and 216 and 218 (M+1).

<u>3,3-Bis(hydroxymethyl)oxetane (24)</u>



24

(a) To a solution of potassium hydroxide (9.8 g) in ethanol (260 ml) in a 1 l. round-bottomed flask, was added 2-(bromomethyl)-2-(hydroxymethyl)propane-1,3-diol (30.0 g, 140 mmol) and the mixture was stirred magnetically for 2 h., then heated under reflux for 5 min. The mixture was cooled and filtered and the filtrate was neutralised with glacial acetic acid and the whole was evaporated at 80°C / 12 mmHg. Distillation of the residue yielded 3,3-bis(hydroxymethyl)oxetane (2.0 g, 11.2%), b.p. 138-142°C / 1 mmHg (Lit.,[22] 155°C / 3.5 mmHg).

υ_{max} 3368 (OH), 1035, 968 and 918 cm^{-1} (oxetane ring).

δ_H 2.6 (bs, 2H, O<u>H</u>), 4.00 (s, 4H, C<u>H</u>$_2$OH), and 4.45 (s, 4H, oxetane ring).

M/Z 119 (M+1), and 136 (M+18).

(b) To a magnetically-stirred solution of potassium hydroxide (0.2 g) in ethanol (5.0 ml) in a 100 ml. round-bottomed flask set up for downward distillation through a 6" Vigreux column, was added diethyl carbonate (13.0 g, 110 mmol) and pentaerythritol (13.6 g, 100 mmol). The mixture was heated with continuous removal of ethanol (b.p. 78-79°C), and when the pot temperature reached 140°C the mixture was cooled and then distilled under reduced pressure. When the pot temperature reached 170°C, carbon dioxide was evolved and the product (4.0 g, 34%) was obtained as a waxy solid, b.p.

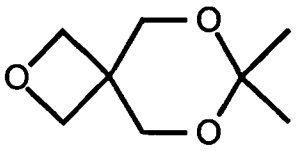
145-160°C / 1 mmHg (Lit.,[22] 155°C / 3.5 mmHg), single spot pure (t.l.c.).

υ_{max} 3375 (OH), 1035, 969 and 917 cm^{-1} (oxetane ring).

δ_H 2.45 (t, 2H, O<u>H</u>), 4.00 (d, 4H, C<u>H</u>$_2$OH), and 4.45 (s, 4H, oxetane ring).

M/Z 119 (M+1), and 136 (M+18).

<u>7,7-Dimethyl-2,6,8-trioxaspiro[3.5]nonane (**160**)</u>



160

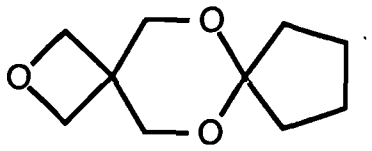
To a solution of 3,3-bis(hydroxymethyl)oxetane (0.59 g, 5.0 mmol) in acetone (10.0 ml) in a 25 ml. round-bottomed flask, was added anhydrous copper (II) sulphate (1.0 g). The mixture was magnetically-stirred at room temperature for 2 days then column chromatographed. Elution with chloroform / methanol (10:1) gave 7,7-dimethyl-2,6,8-trioxaspiro[3.5]nonane (0.60 g, 76%) as a colourless oil.

υ_{max} 977 and 933 cm^{-1} (oxetane ring).

δ_H 1.36 (s, 6H, 2 x C<u>H</u>$_3$), 4.0 (s, 4H, H-5 and H-9), and 4.43 (s, 4H, H-1 and H-3).

M/Z 159 (M+1), and 176 (M+18).

2,6,12-Trioxadispiro[3.2.4.2]tridecane (**161**)



161

To a solution of 3,3-bis(hydroxymethyl)oxetane (0.59 g, 5.0 mmol) in tetrahydrofuran (5 ml) in a 25 ml. round-bottomed flask, were added 4Å molecular sieves (1g), cyclopentanone (0.46 g, 5.5 mmol) and *p*-toluenesulphonic acid (50 mg). The mixture was magnetically-stirred at 0°C for 60 min. and the crude product was column chromatographed. Elution with chloroform / methanol (10:1) gave 2,6,12-trioxadispiro[3.2.4.2]tridecane (0.84 g, 90%) as a colourless oil.

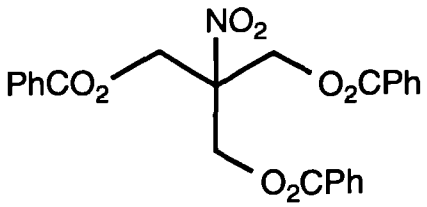
υ_{max} 974 and 930 cm^{-1} (oxetane ring).

δ_H 1.63 (m, 4H, H-9 and H-10), 1.82 (m, 4H, H-8 and H-11), 3.98 (s, 4H, H-5 and H-13), and 4.43 (s, 4H, H-1 and H-3).

M/Z 185 (M+1), and 202 (M+18).

THE PREPARATION OF 3-(HYDROXYMETHYL)OXETANE AND RELATED COMPOUNDS

1,3-Dibenzoyloxy-2-(benzoyloxymethyl)-2-nitropropane (**182**)



182

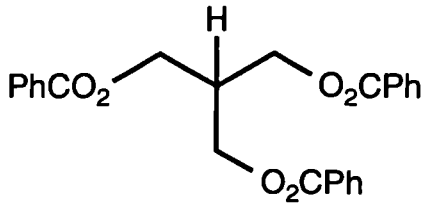
To a magnetically-stirred solution of 2-(hydroxymethyl)-2-nitro-1,3-propanediol (2.1 g, 14 mmol) in pyridine (20 ml) at 0°C in a 100 ml. round-bottomed flask, was added benzoyl chloride (6.8 g, 48 mmol) dropwise keeping the temperature at 0°C. When addition was complete (approx. 20 min), the solution was heated at 70°C for 15 h. then was allowed to cool. Water (60 ml) was added, and the mixture was extracted with dichloromethane (3 x 100 ml). The combined extract was washed successively with saturated aqueous copper (II) sulphate (180 ml) and water (80 ml), then dried and evaporated. Crystallisation of the solid residue from 95% ethanol (50 ml) gave 1,3-dibenzoyloxy-2-(benzoyloxymethyl)-2-nitropropane (3.1 g, 48%), as white needles, m.p. 108-109°C (Lit.,[71] 109-110°C).

υ_{max} 1710 cm^{-1} (ester).

δ_H 5.0 (s, 6H, 3 x $C\underline{H}_2$), and 7.4-8.1 (m, 15H, 3 x $C_6\underline{H}_5$).

M/Z 481 (M+18).

1,3-Dibenzoyloxy-2-(benzoyloxymethyl)propane (183)



183

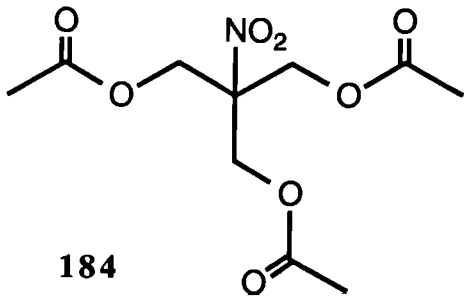
To a magnetically-stirred solution of 1,3-dibenzoyl-2-(benzoyloxymethyl)-2-nitropropane (934 mg, 2.0 mmol) and azobis(isobutyronitrile) (73 mg, 0.44 mmol) in benzene (100 ml), in a flame-dried 250 ml. round-bottomed flask fitted with a reflux condenser and under an atmosphere of dry argon, was added tributylstannane (1.08 g, 3.72 mmol). The solution was heated under reflux for 18 h., then further tributyl-stannane (1.08 g) and azobis(isobutyronitrile) (73 mg) were added and refluxing was continued for a further 24 h. The solvent was removed *in vacuo* and the residue was dissolved in acetonitrile (100 ml). The solution was washed with hexane (5 x 50 ml) and then evaporated to yield a white solid which was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave 1,3-dibenzoyloxy-2-(benzoyloxymethyl)propane (480 mg, 50%) as a white solid, m.p. 75-76°C (Lit.,[71] 75-76°C).

υ_{max} 1716 cm^{-1} (ester).

δ_H 2.8-3.0 (m, 1H, C<u>H</u>$(CH_2)_3$), 4.6 (d, 6H, CH(C<u>H</u>$_2)_3$), and 7.4-8.1 (m, 15H, 3 x C_6<u>H</u>$_5$).

M/Z 436 (M+18).

1,3-Diacetoxy-2-(acetoxymethyl)-2-nitropropane (**184**)



184

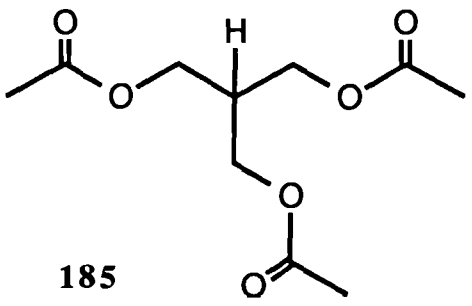
To a magnetically-stirred solution of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (5.2 g, 34 mmol) and triethylamine (20.8 g, 206 mmol) in benzene (40 ml) in a 100 ml round-bottomed flask under an argon atmosphere, was added acetyl chloride (8.9 g, 113 mmol) dropwise. The mixture was allowed to stir at room temperature for 72 h. after which time the solvent was removed *in vacuo*. The solid residue was dissolved in water (100 ml) and the solution was extracted with ethyl acetate (3 x 50 ml). Evaporation of the combined organic extract gave the crude product which was purified by column chromatography. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) afforded 2-(acetoxymethyl)-1,3-diacetoxy-2-nitropropane (3.8 g, 14 mmol, 40%) as colourless prisms, m.p. 72-73°C.

υ_{max} 1238 (acetate), 1388 and 1559 (RNO_2), and 1748 cm^{-1} (acetate).

δ_H 2.1 (s, 9H, 3 x $C\underline{H}_3CO_2$), and 4.6 (s, 6H, 3 x $C\underline{H}_2O_2C$).

M/Z 295 (M+18).

1,3-Diacetoxy-2-(acetoxymethyl)propane (185)



185

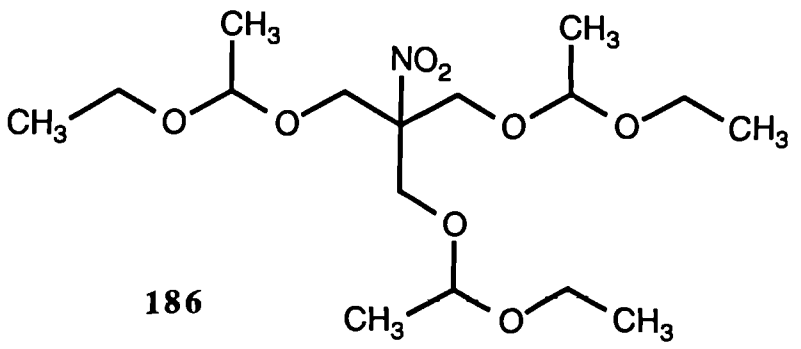
A magnetically-stirred solution of 1,3-diacetoxy-2-(acetoxymethyl)-2-nitro-propane (2.77 g, 10 mmol) in benzene (100 ml) was heated under reflux in a 250 ml round-bottomed flask under an argon atmosphere. Azobis(isobutyronitrile) (365 mg, 2.2 mmol) was added followed by tri-*n*-butyltin hydride (5.41 g, 19 mmol) dropwise over a period of 1 h. The mixture was heated under reflux for a further 24 h., after which time the solvent was removed *in vacuo*. The residual viscous oil was dissolved in acetonitrile (100 ml) and the solution was washed with pentane (4 x 50 ml) then evaporated *in vacuo*. The pale yellow oil obtained was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (4:1) yielded 1,3-diacetoxy-2-(acetoxymethyl)propane (1.3 g, 5.6 mmol, 56%) as a colourless oil.

υ_{max} 1226, and 1742 cm^{-1} (acetate).

δ_H 2.0 (s, 9H, 3 x $C\underline{H}_3CO_2$), 2.4 (m, 1H, $C\underline{H}(CH_2R)_3$, and 4.1 (d, 6H, 3 x $C\underline{H}_2O$).

M/Z 233 (M+1), and 250 (M+18).

1,3-Bis-(1-ethoxyethoxy)-2-(1-ethoxyethoxymethyl)-2-nitropropane (186)



186

To a magnetically-stirred suspension of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (15.1 g, 100 mmol) and *p*-toluenesulphonic acid (250 mg) in diethyl ether (100 ml) in a 250 ml round-bottomed flask fitted with a reflux condenser, was added ethyl vinyl ether* (7.9 g, 110 ml) dropwise and at a rate such that the temperature remained below 40°C. When addition was complete (approx. 15 min) and all of the starting material had dissolved, solid sodium hydrogen carbonate (1.0 g) was added. The solution was washed with water (2 x 50 ml), dried and evaporated to yield 1,3-bis-(1-ethoxyethoxy)-2-(1-ethoxyethoxymethyl)nitropropane (36.3 g, 99 mmol, 99%) as a pale yellow oil.

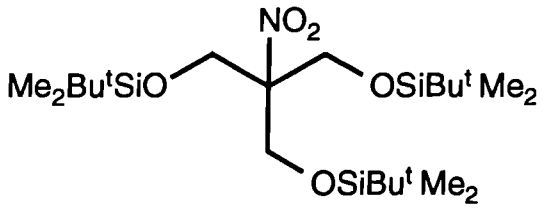
* Ethyl vinyl ether was freshly distilled from sodium before use.

υ_{max} 1554 cm^{-1} (RNO_2).

δ_H 1.15 (t, 9H, 3 x $C\underline{H}_3CH_2$), 1.24 (d, 9H, 3 x $C\underline{H}_3CH$), 3.4-3.6 (m, 6H 3 x $CH_3C\underline{H}_2O$), 3.8-3.9 (m, 6H, $(RC\underline{H}_2)_3NO_2$), and 4.7 (dq, 3H, 3 x $CH_3C\underline{H}(OR)_2$).

M/Z 385 (M+18).

1,3-Bis-(*t*-butyldimethylsilyloxy)-2-(*t*-butyldimethylsilyloxymethyl)-2-nitropropane (187)



187

To a magnetically-stirred solution of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (1.51 g, 10 mmol) and imidazole (5.10 g, 75 mmol) in *N,N*-dimethylformamide (50 ml) in a 100 ml round-bottomed flask and under an argon atmosphere, was added *t*-butyldimethylsilyl chloride (5.64 g, 37 mmol). The mixture was stirred for 24 h. then extracted with pentane (4 x 50 ml). The combined extract was dried and evaporated, and the residual white solid was recrystallised from ethyl acetate to give 1,3-bis-(*t*-butyldimethylsilyloxy)-2-(*t*-butyldimethylsilyloxymethyl)-2-nitropropane (3.3 g, 6.7 mmol, 9%) as a white solid, m.p. 39-41°C.

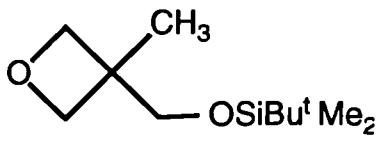
υ_{max} 814 ($SiCH_3$), 1097 (SiOC), 1259 ($SiCH_3$), 1362 and 1553 cm-1 (RNO_2).

δ_H 0.0 (s, 18H, 6 x $SiC\underline{H}_3$), 0.9 (s, 27H, 3 x $SiC(C\underline{H}_3)_3$), and 3.4 (s, 6H, 3 x CH_20).

CHN Found (%) C = 53.39, H = 10.61, and N = 2.87. Required (%) C = 53.50, H = 10.41, and N = 2.84.

M/Z 494.3156 ($C_{22}H_{52}NO_5Si_3$ = 494.5153).

3-(*t*-Butyldimethylsilyloxymethyl)-3-methyloxetane (188)



188

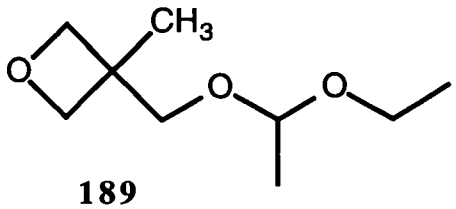
To a magnetically-stirred solution of 3-(hydroxymethyl)-3-methyloxetane (2.04 g, 20 mmol) and imidazole (3.40 g, 50 mmol) in *N,N*-dimethylformamide (10 ml) in a 50 ml round-bottomed flask under an argon atmosphere, was added *t*-butyldimethylsilyl chloride (4.0 g, 30 mmol) portionwise over a period of 10 min. The mixture was allowed to stir for 48 h. before being extracted with pentane (4 x 10 ml). The combined organic extract was dried and evaporated. The residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave 3-(*t*-butyldimethylsilyloxymethyl)-3-methyloxetane (4.2 g, 19 mmol, 97%) as a pale yellow oil.

υ_{max} 836 ($SiCH_3$), 972 (oxetane), 1064 (SiOC), and 1257 cm^{-1} ($SiCH_3$).

δ_H 0.0 (s, 6H, 2 x $C\underline{H}_3$), 0.8 (s, 9H, $SiC(C\underline{H}_3)_3$), 1.2 (s, 3H, $CR_3C\underline{H}_3$), 3.6 (s, 2H, $SiOC\underline{H}_2$), and 4.2-4.5 (m, 4H, oxetane).

M/Z 217 (M+1), and 234 (M+18).

3-(1-Ethoxyethoxymethyl)-3-methyloxetane (189)



189

To a magnetically-stirred solution of 3-(hydroxymethyl)-3-methyloxetane (5.1 g, 50 mmol) and *p*-toluenesulphonic acid (100 mg) in diethyl ether (10 ml) in a 25 ml

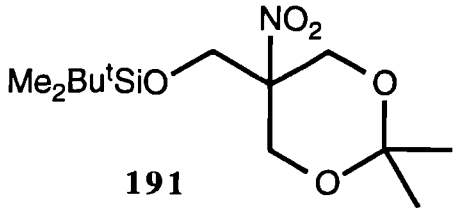
round-bottomed flask under an argon atmosphere, was added ethyl vinyl ether (5.4 g, 75 mmol) dropwise and at a rate such that the temperature remained below 35°C. When the addition was complete (approx 25 min.) the mixture was stirred at room temperature for a further 1 h. before being dissolved in diethyl ether (50 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate (2 x 25 ml) and water (25 ml), then dried and evaporated. The residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (16:1) gave 3-(1-ethoxy-ethoxymethyl)-3-methyloxetane (8.1 g, 46 mmol, 92%) as a colourless oil.

υ_{max} 980 (oxetane), and 1059, 1087 and 1135 cm^{-1} (ethers).

δ_H 1.1 (t, 3H, $CH_2C\underline{H}_3$), 1.2 (d, 3H, $CHC\underline{H}_3$), 1.22 (s, 3H, $CR_3C\underline{H}_3$), 3.3 (m, 2H, $OC\underline{H}_2CH_3$), 3.5 (m, 2H, $CR_3C\underline{H}_2O$), 4.2 (d, 2H, oxetane), 4.4 (d, 2H, oxetane), and 4.6 (q, 1H, $OC\underline{H}(CH_3)O$).

M/Z 179 (M+1), and 192 (M+18).

2,2-Dimethyl-5-(*t*-butyldimethylsilyloxymethyl)-5-nitro-1,3-dioxane (**191**)



191

To a magnetically-stirred solution of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (3.02 g, 20 mmol) and *p*-toluenesulphonic acid (100 mg) in *N,N*-dimethylformamide (25 ml) in a 50 ml round-bottomed flask under an argon atmosphere, was added 2-methoxypropene (1.40 g, 20 mmol) dropwise and at a rate such that the temperature remained below 35°C. When addition was complete (approx. 15 min), the reaction was allowed to stir for a further 1 h. Imidazole (3.5 g, 50 mmol) and *t*-butyldimethylsilyl chloride (3.4 g, 24 mmol) were added and the reaction was stirred at room temperature for a further 24 h. The solvent was the removed *in vacuo* and the residue was column

chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (25:1) afforded 2,2-dimethyl-5-(*t*-butyldimethylsilyloxymethyl)-5-nitro-1,3-dioxane (1.35 g, 4.4 mmol, 22%) as a white solid, m.p. 59-60°C.

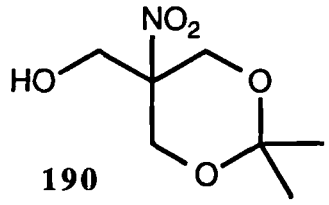
υ_{max} 837 and 1259 ($SiCH_3$), and 1378 and 1549 cm^{-1} (RNO_2).

δ_H 0.0 (s, 6H, 2 x $SiC\underline{H}_3$), 0.9 (s, 9H, $SiC(C\underline{H}_3)_3$), 1.4 (s, 6H, 2 x $C\underline{H}_3$), 4.0 (s, 2H, $C\underline{H}_2O$), and 4.0-4.5 (dd, 4H, ring).

CHN Found (%) C = 50.90, H = 8.88, and N = 4.41. Required (%) C = 51.12, H = 8.91, and N = 4.59.

M/Z Found 323.2002 ($C_{13}H_{31}N_2O_5Si$ = 323.2002).

2,2-Dimethyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane (**190**)



190

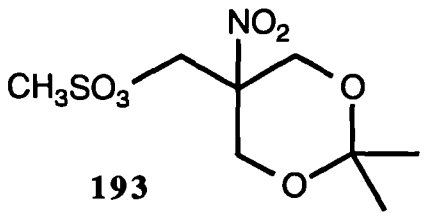
To a magnetically-stirred solution of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (3.02 g, 20 mmol) and *p*-toluenesulphonic acid (100 mg) in *N,N*-dimethylformamide (25 ml) in a 50 ml round-bottomed flask and under an argon atmosphere, was added 2-methoxypropene (1.40 g, 20 mmol) dropwise and at a rate such that the temperature remained below 35°C. When addition was complete (approx. 15 min) the reaction was allowed to stir for a further 1 h. Solid sodium hydrogen carbonate (0.5 g) was added and the solvent was removed *in vacuo*. The residue was stirred with ethyl acetate (50 ml) and the resulting slurry was washed with water (2 x 10 ml) then dried and evaporated. The residue was recrystallised from ethanol and gave 2,2-dimethyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane (2.4 g, 12.6 mmol, 63%) as white prisms, m.p. 133.5-134°C (Lit.,[80] 133-134.5°C).

υ_{max} 1386 and 1544 (RNO_2), and 3428 cm^{-1} (OH).

δ_H 1.4 (d, 6H, 2 x $C\underline{H}_3$), 4.0 (d, 2H, $C\underline{H}_2O$), and 4.1-4.4 (dd, 4H, ring).

M/Z 192 (M+1), and 209 (M+18).

2,2-Dimethyl-5-(methanesulphonyloxymethyl)-5-nitro-1,3-dioxane (193)



193

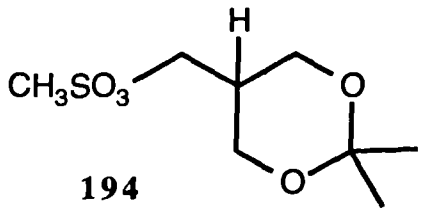
To a magnetically-stirred solution of 2.2-dimethyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane (3.82 g, 20.0 mmol) in pyridine (50 ml) in a 100 ml round-bottomed flask and under an argon atmosphere, was added methanesulphonyl chloride (2.52 g, 22 mmol) dropwise over a period of 5 min. After stirring for 24 h., the solvent was removed and the residue was dissolved in ethyl acetate (100 ml). The solution was washed successively with saturated aqueous copper (II) sulphate (2 x 50 ml), dilute aqueous ammonium hydroxide (2 x 50 ml) and saturated aqueous sodium chloride (50 ml) then dried and evaporated. The residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (4:1) gave 2,2-dimethyl-5-(methane-sulphonyloxymethyl)-5-nitro-1,3-dioxane as a white crystalline solid (4.6 g, 17.0 mmol, 85%), m.p. 73-4°C.

υ_{max} 1184 and 1362 (RSO_3R'), and 1381 and 1555 cm^{-1} (RNO_2).

δ_H 1.3 (s, 6H, 2 x $C\underline{H}_3$), 2.9 (s, 3H, $C\underline{H}_3SO_3$), 3.9-4.4 (dd, 4H, ring), and 4.6 (s, 2H, $CH_3SO_3C\underline{H}_2R$).

M/Z Found 287.0927 ($C_8H_{19}N_2O_7S$ = 287.0913).

2,2-Dimethyl-5-(methanesulphonyloxymethyl)-1,3-dioxane (194)



194

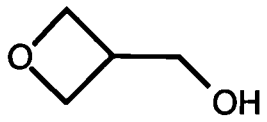
A magnetically-stirred solution of 2,2-dimethyl-5-(methanesulphonyloxymethyl)-5-nitro-1,3-dioxane (2.69 g, 10 mmol) in benzene (100 ml) was heated under reflux in a 250 ml round-bottomed flask under an argon atmosphere. Azobis(isobutyronitrile) (365 mg, 2.2 mmol) was added followed by tri-*n*-butyltin hydride (5.41 g, 19 mmol), dropwise, over a period of 1 h., and the reaction was heated under reflux for a further 24 h. The solvent was removed *in vacuo* and the residual oil was dissolved in acetonitrile (100 ml). The solution was washed with pentane (4 x 50 ml) and the solvent was removed *in vacuo*. The pale yellow oil obtained was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (4:1) yielded 2,2-dimethyl-5-(methanesulphonyloxymethyl)-5-nitro-1,3-dioxane (1.46 g, 6.5 mmol, 65%) as a colourless oil.

υ_{max} 1175 and 1356 cm^{-1} (RSO_3R').

δ_H 1.3 (s, 3H, $C\underline{H}_3$), 1.4 (s, 3H, $C\underline{H}_3$), 2.0 (m, 1H, $C\underline{H}(CH_2R)_3$), 3.0 (s, 3H, $C\underline{H}_3SO_3$), 3.7-4.0 (dd, 4H, ring), and 4.4 (d, 2H, $CH_3SO_3C\underline{H}_2R$).

M/Z Found 225.0767 ($C_8H_{17}O_5S$ = 225.0793).

3-(Hydroxymethyl)oxetane (**126**)



126

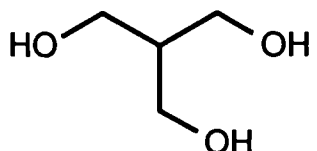
Hydrochloric acid (1M, 5 ml) was magnetically stirred in a 25 ml round-bottomed flask fitted with a reflux condenser whilst 2,2-dimethyl-5-(methane-sulphonyloxymethyl)-5-nitro-1,3-dioxane (100 mg, 450 μmol) was added dropwise. When solution was complete, sodium hydroxide (5.0 g) was added and the mixture was allowed to cool to room temperature. The mixture was then added to water (50 ml), and the product was extracted with dichloromethane (4 x 25 ml). The combined extract was dried and evaporated. The residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave 3-(hydroxymethyl)oxetane (14 mg, 160 μmol, 35%) as a pale yellow oil

υ_{max} 968 and 1022 cm^{-1} (oxetane).

δ_H 3.1 (m, 1H, H-3_α), 3.2 (bs, 1H, O<u>H</u>), 3.5 (d, 2H, C<u>H_2</u>OH), (dd, 2H, H-2_α and H-4_α), and 4.4 (dd, 2H, H-2_β and H-4_β).

M/Z 89 (M+1), and 106 (M+18).

2-(Hydroxymethyl)propane-1,3-diol (**163**)



163

To a magnetically-stirred solution of sodium hydroxide (2.0 g, 50 mmol) and 2-amino-2-(hydroxymethyl)propane-1,3-diol (2.42 g, 20 mmol) in a 250 ml conical flask

with ice-water cooling, was added hydroxylamine-*O*-sulphonic acid (4.85 g, 42.7 mmol) portionwise and over a period of 30 min. (Each addition was accompanied by vigorous effervescence.) When all sign of reaction had ceased (approx. 30 min), aqueous sodium hydroxide [sodium hydroxide (1.0 g, 25 mmol) in water (20 ml)] was added. Hydroxylamine-*O*-sulphonic acid (2.43 g, 21.4 mmol) was then added portionwise over a period of 15 min. and when all effervescence had ceased (approx. 30 min), the solvent was removed *in vacuo*. The residue was added to hot ethanol (100 ml) and the resulting mixture was magnetically-stirred under reflux for 1 h. The mixture was then dried and filtered, and the filtrate was evaporated to give crude 2-(hydroxymethyl)propane-1,3-diol as a pale yellow oil (1.70 g, 16.4 mmol, 82%). Crystallisation of this oil, by freezing and allowing to thaw slowly, yielded a small amount of solid product which was isolated from the oil by pressing the mixture between two filter papers. Recrystallisation of the solid from acetone yielded 2-(hydroxymethyl)propane-1,3-diol (135 mg, 1.1 mmol, 6%) as a white crystalline solid, m.p. 66-9°C (Lit.,[70] 67-8°C).

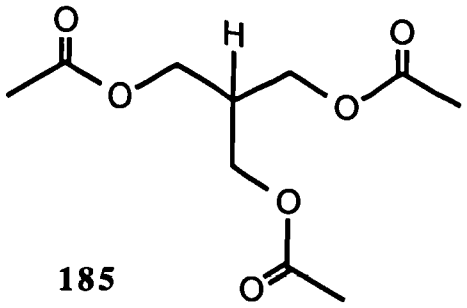
υ_{max} 3277 cm^{-1} (OH).

δ_H (m, 1H, C<u>H</u>$(CH_2OH)_3$), 3.6 (d, 6H, CH(C<u>H</u>$_2$OH)$_3$), and 4.8 (bs, 3H, CH(CH_2O<u>H</u>)$_3$).

CHN Found (%) C = 43.94, H = 9.76, and N = 0.50. Required (%) C = 45.27, H = 9.50, and N = 0.00.

M/Z 119 (M+1), and 135 (M+18).

1,3-Diacetoxy-2-(acetoxymethyl)propane (185)



185

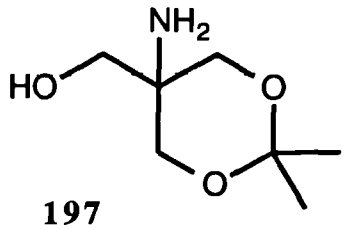
To a magnetically-stirred solution of sodium hydroxide (2.0 g, 50 mmol) and 2-amino-2-(hydroxymethyl)propane-1,3-diol (2.42 g, 20 mmol) in a 250 ml conical flask with ice-water cooling, was added hydroxylamine-*O*-sulphonic acid (4.85 g, 42.7 mmol) portionwise and over a period of 30 min. (Each addition was accompanied by vigorous effervescence.) When all sign of reaction had ceased (approx. 30 min), aqueous sodium hydroxide [sodium hydroxide (1.0 g, 25 mmol) in water (20 ml)] was added. Hydroxylamine-*O*-sulphonic acid (2.43 g, 21.4 mmol) was then added portionwise over a period of 15 min. and when all effervescence had ceased (approx. 30 min), the solvent was removed *in vacuo*. The residue was added to hot ethanol (100 ml) and the resulting mixture was magnetically-stirred under reflux for 1 h. The mixture was then dried and filtered, and the filtrate was evaporated to give crude 2-(hydroxymethyl)propane-1,3-diol as a pale yellow oil (1.70 g, 16.4 mmol, 82%).

The oil was added to a refluxing solution of sodium acetate (5.0 g, 61 mmol) and acetic anhydride (5.0 g, 37 mmol) in acetic acid (25 ml) and refluxing was continued for a further 24 hours. Ethyl acetate (250 ml) was then added, followed by solid sodium hydrogen carbonate (40g). The mixture was washed with water (3 x 100 ml) then dried and evaporated. The residual oil was Kugelrohr distilled, and gave 1,3-diacetoxy-2-(acetoxymethyl)propane (1.87 g, 8.1 mmol, 40%) as a colourless oil, b.p. 260°C.

υ_{max} 1232, and 1739 cm^{-1} (acetate).

δ_H 2.0 (s, 9H, 3 x $C\underline{H}_3CO_2$), 2.4 (m, 1H, $C\underline{H}(CH_2R)_3$, and 4.1 (d, 6H, 3 x $C\underline{H}_2O$).
M/Z 250 (M+18).

5-Amino-2,2-dimethyl-5-(hydroxymethyl)-1,3-dioxane (**197**)



197

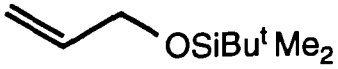
5% Palladium on carbon (1 g) was added to a solution of 2,2-dimethyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane (0.96 g, 5.0 mmol) in ethanol (250 ml). The mixture was shaken under hydrogen at a pressure of 100 atmospheres at 70°C for 2 h., after which time the mixture was cooled and filtered through Celite® 521. The filtrate was evaporated *in vacuo* to yield 5-amino-2,2-dimethyl-5-(hydroxymethyl)-1,3-dioxane (8.0 mg, 5.0 mmol, 100%) as a white solid, m.p. 54-5°C.

υ_{max} 3300 (OH), 3335 and 3340 cm^{-1} (NH_2).

δ_H 1.3 (s, 3H, $C\underline{H}_3$), 1.4 (s, 3H, $C\underline{H}_3$), 1.8 (bs, 1H, O$\underline{H}$), 3.5 (s, 2H, $C\underline{H}_2OH$), and 3.6-3.8 (dd, 4H, ring).

M/Z 162 (M+1), and 179 (M+18).

Allyl *t*-butyldimethylsilyl ether (**203**)



203

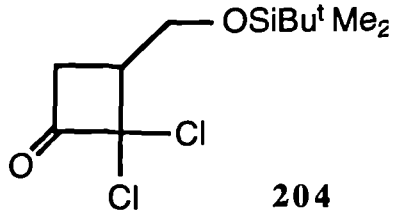
To a magnetically-stirred solution of allyl alcohol (3.24 ml, 47.6 mmol) and *N,N*-diisopropylethylamine (14.4 ml, 80.4 mmol) in dichloromethane (15 ml) in a 100

ml. round-bottomed flask, at 0°C, was added *t*-butyldimethylsilyl chloride (10.0 g, 66.4 mmol) portionwise and at a rate such that the temperature remained at 0°C (ice / salt cooling). When addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24 h. Water (20 ml) was then added and after stirring for 10 min., the mixture was further diluted with water (120 ml). The solution was extracted with dichloromethane (4 x 40 ml) and the combined extract was washed with saturated aqueous ammonium chloride (50 ml), then dried and evaporated. The residual oil was Kugelrohr distilled, and gave *t*-butyldimethylsilyl ether (11.45 g, 39%) as a colourless oil.

υ_{max} 1647, 1253, and 834 cm^{-1}.

δ_H 0.05 (s, 6H, $Si(C\underline{H}_3)_2$), 0.90 (s, 9H, $SiC(C\underline{H}_3)_3$), 4.15 (m, 2H, $C\underline{H}_2O$), 5.05 (m, 1H, H-trans), 5.25 (m, 1H, H-cis), and 5.90 (m, 1H, H-gem).

3-(*t*-Butyldimethylsilyloxymethyl)-2,2-dichlorocyclobutanone (**204**)



204

A dry, 3-necked, 50 ml. flask fitted with a condenser, dropping funnel, and a nitrogen inlet, was dried and purged with nitrogen. In the flask was placed a mixture of allyl *t*-butyldimethylsilyl ether (1.65 g, 9.60 mmol), activated zinc (0.69 g, 10.5 mmol) (for preparation see below) and anhydrous diethyl ether (20 ml). The mixture was stirred under a nitrogen atmosphere whilst a solution of trichloroacetyl chloride (1.83 g, 10.0 mmol) and phosphorous oxychloride (1.53 g, 10.0 mmol) in anhydrous diethyl ether (5 ml) was added dropwise over a period of 1 h. The mixture was heated under reflux for 2 h., then cooled and filtered through Celite® 521 filter aid. The unreacted zinc was washed with anhydrous diethyl ether (25 ml) and the combined organic

solution was concentrated to 15 ml. when pentane (15 ml) was added. The resulting mixture was filtered, and the filtrate was washed sequentially with water (25 ml), saturated aqueous sodium hydrogen carbonate (25 ml), saturated aqueous sodium chloride (25 ml) then dried and evaporated. The residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave 3-(*t*-butyldimethylsilyloxymethyl)-2,2-dichlorocyclobutanone (1.59 g, 59%) as a colourless oil.

υ_{max} 1816 (cyclobutanone) and 838 cm^{-1} (C-Cl).

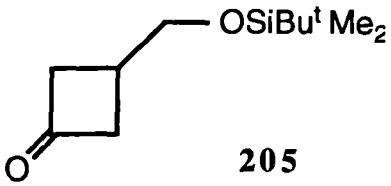
δ_H 0.05 (s, 6H, $Si(C\underline{H}_3)_2$), 0.90 (s, 9H, $SiC(C\underline{H}_3)_3$), 3.10 (m, 2H, H-4α+β), 3.4 (m, 1H, H-3), and 3.95 (d, 2H, $C\underline{H}_2O$).

M/Z 300, 302, and 304 (M+18).

Activated zinc.

Through a mechanically-stirred suspension of zinc dust (10.0 g, 150 mmol) in water (40 ml) was bubbled nitrogen for 15 min. Copper (II) sulphate (750 mg, 4.7 mmol) was then added, and bubbling was continued through the resulting black suspension for a further 45 min. The zinc-copper couple was collected by filtering through a glass sinter under a stream of nitrogen and then washed sequentially with degassed water (100 ml) and anhydrous acetone (100 ml). It was dried *in vacuo* and stored under nitrogen.

3-(*t*-Butyldimethylsilyloxymethyl)cyclobutanone (205)



205

To a magnetically-stirred mixture of zinc dust (307 mg, 4.60 mmol) and

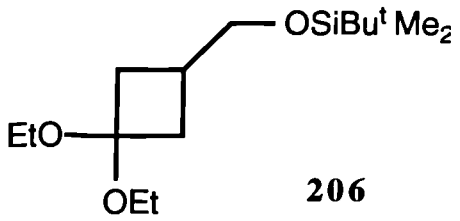
ammonium chloride (113 mg, 4.60 mmol) in methanol (1.3 ml) in a 10 ml round-bottomed flask at 0°C, was added dropwise 2,2-dichloro-3-(*t*-butyldimethylsilyloxy-methyl)cyclobutanone (142 mg, 500 μmol). When addition was complete, the mixture was allowed to warm to room temperature and stirring was maintained until no starting material could be observed by t.l.c. (approx. 24 h). The mixture was filtered and the residue was washed with methanol (2 x 1 ml). The combined filtrate and washings was diluted with water (10 ml) and the mixture was extracted with diethyl ether (3 x 5 ml). The combined extract was dried and evaporated and the residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave 3-(*t*-butyldimethylsilyloxymethyl)cyclobutanone (22 mg, 21%) as a colourless oil.

υ_{max} 1785 cm^{-1} (cyclobutanone).

δ_H 0.05 (s, 6H, $Si(C\underline{H}_3)_2$), 0.90 (s, 9H, $SiC(C\underline{H}_3)_3$), 2.55 (m, 1H, H-3), 2.8-3.1 (m, 4H, H-$2_{\alpha+\beta}$ and H-$4_{\alpha+\beta}$), and 3.7 (d, 2H, $C\underline{H}_2O$).

M/Z 232 (M+18).

3-(*t*-Butyldimethylsilyloxymethyl)-1,1-diethoxycyclobutane (**206**)



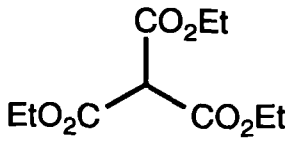
206

A solution of 3-(*t*-butyldimethylsilyloxymethyl)cyclobutanone (22 mg, 102 μmol) and *p*-toluenesulphonic acid (5 mg) in ethanol (10 ml) was magnetically stirred over 4Å molecular sieves (100 mg) for 24 h. Solid sodium hydrogen carbonate (3 mg) was added and the mixture was filtered. The filtrate was evaporated and the residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave 3-(*t*-butyldimethylsilyloxymethyl)-1,1-diethoxycyclobutane (22 mg, 73%) as a colourless oil.

υ_{max} 2858 and 1090 cm^{-1} (acetal).

δ 0.05 (s, 6H, $Si(C\underline{H}_3)_2$), 0.90 (s, 9H, $SiC(C\underline{H}_3)_3$), 1.15 (m, 6H, 2 x $C\underline{H}_3CH_2O$), 1.85 (m, 2H, H-2_α and H-4_α), 2.20 (m, 3H, H-2_β, H-3_α and H-4_β), 3.35 (m, 4H, 2 x $CH_3C\underline{H}_2O$), and 3.60 (d, 2H, $C\underline{H}_2O$).

Triethyl methanetricarboxylate (211)



211

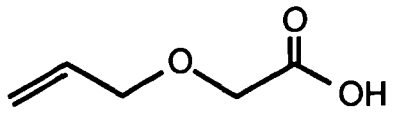
A mixture of light magnesium oxide (4.0 g, 100 mmol), toluene (10 ml), diethyl malonate (8.0 ml, 52 mmol) and ethyl chloroformate (4.0 ml, 40 mmol) in a 100 ml. round-bottomed flask fitted with a reflux condenser, was mechanically stirred at 80°C for 6 h. The mixture was cooled to 0°C and water was added dropwise until the fine white precipitate coagulated. The supernatant liquid was decanted and the precipitate was washed with diethyl ether (10 ml). The ethereal solution was decanted and the two organic solutions were combined. The residual solid was dissolved in the minimum volume of 5M hydrochloric acid (with ice-water cooling) and the solution was extracted with diethyl ether (2 x 10 ml). These extracts were united with the previous organic solutions. The combined extract was washed sequentially with 1M hydrochloric acid (30 ml), water (30 ml), 5% aqueous sodium hydrogen carbonate (30 ml) and saturated aqueous sodium chloride (30 ml), then dried and evaporated to give a colourless oil (8.3 g), which on distillation gave triethyl methanetricarboxylate (4.1 g, 44%) as a colourless oil, b.p. 132-4°C / 12 mmHg (Lit.,[76] 135-137°C / 12 mmHg).

υ_{max} 1739 cm^{-1} (ester).

δ_H 1.3 (t, 9H, 3 x $CH_2C\underline{H}_3$), 4.3 (q, 6H, 3 x $OC\underline{H}_2CH_3$), and 4.4 (s, 1H, $C\underline{H}(CO_2Et)_3$).

M/Z 233 (M+1), and 250 (M+18).

2-Allyloxyacetic acid (**214**)



214

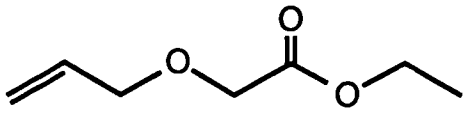
To magnetically-stirred allyl alcohol (120 ml) in a 250 ml round-bottomed flask fitted with a reflux condenser and dropping funnel under an argon atmosphere, was added sodium metal (13.0 g, 565 mmol) portionwise over a period of 1 h. When all of the metal had dissolved (approx. 3 h), a solution of chloroacetic acid (23.0 g, 243 mmol) in allyl alcohol (30 ml) was added dropwise and at a rate such that the reaction mixture refluxed gently. When addition was complete (approx. 4 h), the mixture was allowed to cool and stirring was continued for a further 12 h. Solid carbon dioxide (25 g, 570 mmol) was added to the mixture, and when all reaction had ceased, the mixture was evaporated to dryness. The solid residue was dissolved in water (250 ml) and the solution was extracted with diethyl ether (3 x 150 ml). The combined extract was dried and evaporated to afford allyloxyacetic acid (4.8 g) as a colourless oil, sufficiently pure for use in the next experiment.

υ_{max} 1120 (CH_2OCH_2), 1648 ($CH=CH_2$), 1731 and 3408 cm^{-1} (CO_2H).

δ_H 4.0 (d, 2H, $CH_2=CHC\underline{H}_2O$), 4.1 (s, 2H, $OC\underline{H}_2CO_2H$), 5.1-5.3 (m, 2H, $C\underline{H}_2=CH$), and (m, 1H, $CH_2=C\underline{H}CH_2$).

M/Z 117 (M+1), and 134 (M+18).

Ethyl allyloxyacetate (215)



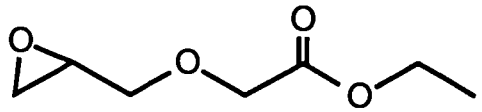
215

To a magnetically-stirred solution of allyloxyacetic acid (4.8 g, 41 mmol) in ethanol (500 ml) in a 1000 ml round-bottomed flask, was added acetyl chloride (1 ml). The mixture was stirred for 48 h., neutralised with solid sodium hydrogen carbonate (5 g). The product was dried over magnesium sulphate and filtered, and the solvent was removed *in vacuo* to give ethyl allyloxyacetate (5.7 g) as a pale yellow oil, sufficiently pure for use in the next experiment.

υ_{max} 1203 (CH_2OCH_2), 1649 (CH_2=CH), and 1755 cm^{-1} (CO_2R).

δ_H 1.3 (t, 3H, $OCH_2C\underline{H}_3$), 3.5-3.8 (m, 2H, $OC\underline{H}_2CO_2$), 4.1-4.3 (m, 4H, $OC\underline{H}_2CH_3$ and CH_2=$CHC\underline{H}_2O$), 5.1-5.4 (m, 2H, $C\underline{H}_2$=CH), and 5.7-6.1 (m, 1H, CH_2=C$\underline{H}$).

Ethyl glycidyloxyacetate (213)



213

(a) To a magnetically-stirred solution of ethyl allyloxyacetate (2.88 g, 20 mmol) in dichloromethane (50 ml) under an argon atmosphere, in a 100 ml round-bottomed flask, was added *m*-chloroperoxybenzoic acid (4.7 g, 30 mmol) and the mixture was stirred for 48 h. The solution was then washed with saturated aqueous sodium hydrogen carbonate (2 x 20 ml), dried and evaporated. The residue was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave ethyl

glycidyloxyacetate (1.92 g, 12 mmol, 60%) as a colourless oil.

υ_{max} 1207 (CH_2OCH_2), 1282 (epoxide), and 1754 cm^{-1} (CO_2R).

δ_H 1.2 (t, 3H, $C\underline{H}_3CH_2$), 2.6 (dd, 1H, epoxide H-*cis*), 2.8 (dd, 1H, epoxide H-*trans*), 3.2 (dd, 1H, epoxide H-*gem*), 3.4 (dd, 1H, glycidyl $C\underline{H}_2$), 3.9 (dd, 1H, glycidyl $C\underline{H}_2$) 4.1 (d, 2H, $OC\underline{H}_2CO_2R$), and 4.2 (q, 2H, $OC\underline{H}_2CH_3$).

M/Z 161 (M+1), and 178 (M+18).

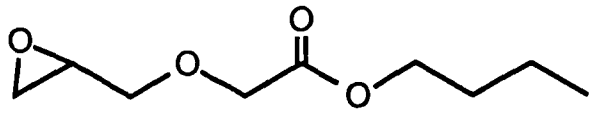
(b) To a magnetically-stirred solution of glycidol (7.2 g, 100 mmol) in tetrahydrofuran (30 ml) in a 100 ml round-bottomed flask fitted with reflux condenser and dropping funnel, under an argon atmosphere, was added a solution of ethyl bromoacetate (16.7 g, 100 mmol) in tetrahydrofuran (20 mmol) dropwise over 30 min. When addition was complete, the mixture was stirred for 24 h., and water (50 ml) was added. The mixture was extracted with diethyl ether (3 x 50 ml) and the combined organic extract was dried and evaporated to afford the crude epoxide as a yellow oil. This was purified by column chromatography. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave ethyl glycidyloxyacetate (10.3 g, 64 mmol, 64%) as a colourless oil.

υ_{max} 1207 (CH_2OCH_2), 1282 (epoxide), and 1754 cm^{-1} (CO_2R).

δ_H 1.2 (t, 3H, $C\underline{H}_3CH_2$), 2.6 (dd, 1H, epoxide H-*cis*), 2.8 (dd, 1H, epoxide H-*trans*), 3.2 (dd, 1H, epoxide H-*gem*), 3.4 (dd, 1H, glycidyl $C\underline{H}_2$), 3.9 (dd, 1H, glycidyl $C\underline{H}_2$) 4.1 (d, 2H, $OC\underline{H}_2CO_2R$), and 4.2 (q, 2H, $OC\underline{H}_2CH_3$).

M/Z 161 (M+1), and 178 (M+18).

Butyl glycidyloxyacatate (219)



219

To a magnetically-stirred solution of di-isopropylamine (111 mg, 1.1 mmol) in diethyl ether (5 ml) in a 25 ml round-bottomed flask under an argon atmosphere, was added a solution of *n*-butyllithium (68 mg, 1.1 mmol) in hexane (750 µl). The mixture was cooled to -78°C (solid carbon dioxide - acetone cooling) and stirred for 10 min. A solution of ethyl glycidyloxyacetate (160 mg, 1.0 mmol) in diethyl ether (1 ml) was cooled to -78°C and then added dropwise with stirring. After stirring at -78°C for a further 1 h., the solution was allowed to warm to room temperature and stirring was continued for a further 24 h. Saturated aqueous ammonium chloride (2 ml) was then added, followed by diethyl ether (25 ml). The mixture was washed with water (10 ml) then saturated sodium chloride solution (10 ml), dried and evaporated. The crude product was column chromatographed. Elution with light petroleum (b.p. 40-60°C) / ethyl acetate (8:1) gave butyl glycidyloxyacetate (28 mg, 0.15 mmol, 15%) as a colourless oil.

υ_{max} 850 (epoxide), 1205 (CH_2OCH_2 stretch), 1279 (epoxide), and 1755 cm^{-1} (CO_2R).

δ_H 0.9 (t, 3H, $C\underline{H}_3CH_2R$), 1.2-1.7 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2R$), 2.6 (dd, 1H, epoxide H-*cis*), 2.8 (dd, 1H, epoxide H-*trans*), 3.2 (m, 1H, epoxide H-*gem*), 3.4 (dd, 1H, glycidyl $C\underline{H}_2$), 3.9 (dd, 1H, glycidyl $C\underline{H}_2$), and 4.1-4.2 (m, 4H, $OC\underline{H}_2CO_2C\underline{H}_2R$).

M/Z 189 (M+1), and 206 (M+18).

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